201-14721A

DIMETHYL SULFOXIDE PRODUCERS ASSOCIATION
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September 8, 2003
Submitted electronically to:
Chem.rtk@epa.gov
Oppt.ncic@epa.gov

Administrator
US Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116
Attention: Chemical Right-to-Know Program

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2003 SEP 9 AM 11:52

RE: Status of Commitment Under U.S. HPV Program - DMSO

This submission is being made on behalf of the Dimethyl Sulfoxide (DMSO) Producers Association regarding DMSO (CAS Number 67-68-5) which is sponsored under the U.S. HPV Challenge Program.

DMSO is used industrially as a reaction solvent, polymerization solvent, in antifreeze, hydraulic fluid, paint and varnish removers, as a pharmaceutical solvent, as an analytical reagent, as a clean-up solvent and in the manufacture of synthetic fibers, industrial cleaners and pesticides. In medicine it is used as a treatment for interstitial cystitis, in the preservation of cells at low temperatures, in the diffusion of drugs into the bloodstream by topical applications, as an anti-inflammatory agent and as an analgesic. It is also used in veterinary medicine. It is used in plant pathology and nutrition. [National Toxicology Program, ntp-db.niehs.nih.gov, and from "The Kirk-Othmer Concise Encyclopedia of Chemical Technology", 4th edition]

DMSO is not a compound for which releases into the environment require reporting under the US-EPA Toxic Release Inventory (TRI). Due to its low vapor pressure, the proportion of releases into air is low. DMSO users often recycle it and thereby limit discharges. DMSO is present in some industrial wastewaters and is readily biodegradable.

DMSO occurs naturally in low levels in many fruits, vegetables, grains and beverages; these include raspberry, corn, oats, coffee, milk and tea. [J.Agric.Food Chem., 29, 1089-1091 (1981).] Consumers may also be exposed to it in the use of pharmaceuticals and other products (See "Uses" above).

The attached IUCLID dossier summarizes the available data for DMSO. The data used to characterize the HPV Challenge endpoints for DMSO were identified either in company proprietary files, the peer-reviewed literature, and/or calculated using widely accepted computer modeling programs.

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I U C L I D

Data Set

Existing Chemical	:	ID: 67-68-5
CAS No.	:	67-68-5
EINECS Name	:	dimethyl sulfoxide
EC No.	:	200-664-3
TSCA Name	:	Methane, sulfinylbis-
Molecular Formula	:	C2H6OS

Producer related part

Company	:	ATOFINA Chemicals Inc.
Creation date	:	28.05.2003

Substance related part

Company	:	ATOFINA Chemicals Inc.
Creation date	:	28.05.2003
Status	:	
Memo	:	
Printing date	:	12.08.2003
Revision date	:	
Date of last update	:	12.08.2003
Number of pages	:	133
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	:	lead organisation
Name	:	Dimethyl Sulfoxide Producers Association
Contact person	:	Betty Hunt
Date	:	
Street	:	941 Rhonda Place SE
Town	:	20175 Lessburg, Va
Country	:	United States
Phone	:	703-669-5688
Telefax	:	
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Cedex	:	
Email	:	ehunt@adelphia.com
Homepage	:	

29.05.2003

Type	:	cooperating company
Name	:	Atofina
Contact person	:	
Date	:	
Street	:	4-8, cours Michelet La Défense 10
Town	:	95091 Paris La Défense Cedex
Country	:	France
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

Source : Atofina Paris La Défense Cedex
28.05.2003

Type	:	cooperating company
Name	:	ATOFINA Chemicals Inc.
Contact person	:	
Date	:	
Street	:	2000 Market Street
Town	:	PA 19103 Philadelphia
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

12.08.2003

Type	:	cooperating company
Name	:	Gaylord Chemical Corporation
Contact person	:	John Ferguson
Date	:	
Street	:	
Town	:	70427 Bogalusa, LA
Country	:	United States
Phone	:	

Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

12.08.2003

Type	:	cooperating company
Name	:	Toray Fine Chemicals Company, Ltd.
Contact person	:	Katsuhiro Shibayama
Date	:	
Street	:	8-1, Mihama 1-chome
Town	:	279-8555 Urayasu, ChibaShiga
Country	:	Japan
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Telefax	:	+81 (47) 350-6091
Telex	:	
Cedex	:	
Email	:	katsuhiro_shibayama@tfc.toray.co.jp
Homepage	:	

10.07.2003

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	
Molecular formula	:	C2H6OS
Molecular weight	:	78.13
Petrol class	:	
Source	:	Atofina, Paris-le-Défense, France. Atofina Paris La Défense Cedex

27.12.2002

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	> 99 % w/w
Colour	:	clear
Odour	:	
Source	:	Atofina, Paris-le-Défense, France. Atofina Paris La Défense Cedex

27.12.2002

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

dimethyl sulphoxide

22.07.2003

Sulfinylbis(methane); methyl sulfoxide; DMSO; SQ 9453; DMS-70; DMS-90; deltan; Demasorb; Demavet; Demeso; Dermasorb; Dolicur; Domoso; Dromisol; Gamasol 90; Hyadur; Infiltrina, Rimso-50; Somipront; Syntexan; Topsym (rescinded)

Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

27.12.2002 (139)

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

Labelling : no labelling required (no dangerous properties)
Specific limits :

Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

09.12.2002

1.6.2 CLASSIFICATION

Classified : no classification required (no dangerous properties)
Class of danger :
R-Phrases :
Specific limits :

Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

09.12.2002

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

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

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : Continuous process. Oxydation of Dimethylsulfide with N2O4/NO2 as catalyst. Purification by distillation after neutralisation (NaOH).
Effluents: water treatment plant
Losses of product can only occur if problem during maintenance

Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

27.12.2002

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External

Chapters covered	:	3, 4, 5
Date of search	:	27.12.2002
Source	:	Atofina, Paris-le-Défense, France. Atofina Paris La Défense Cedex

27.12.2002

1.13 REVIEWS

2.1 MELTING POINT

Value	:	= 18.5 °C
Decomposition	:	no, at °C
Sublimation	:	
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

10.12.2002 (52)

2.2 BOILING POINT

Value	:	= 189 °C at 1013 hPa
Decomposition	:	yes
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	
Remark	:	Start of decomposition : T>190°C Decomposition products : Methane thiol; formaldehyde; dimethyl sulfide and dimethylsulfone.
Source	:	ATOFINA, Paris-La Défense, France. Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions Data from handbook
Flag	:	Critical study for SIDS endpoint

12.12.2002 (125)

2.3 DENSITY

Type	:	density
Value	:	= 1.1 g/cm³ at 20 °C
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	
Source	:	ATOFINA, Paris-La Défense, France. Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

12.12.2002 (119) (128)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .55 hPa at 20 °C
Decomposition	:	

Method : other (calculated): no data
Year :
GLP : no data
Test substance :

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
12.12.2002 (140)

Value : = .81 hPa at 25 °C

Source : ATOFINA, Paris-La Défense, France.
Atofina Paris La Défense Cedex
10.02.2003 (37)

2.5 PARTITION COEFFICIENT

Partition coefficient :
Log pow : = -1.35 at °C
pH value :
Method : other (measured)
Year :
GLP : no data
Test substance :

Source : ATOFINA, Paris-La Défense, France.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Data from handbook
Flag : Critical study for SIDS endpoint
18.09.2000 (68)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Remark : Totally soluble in water.
Source : ATOFINA, Paris-La Défense, France.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Data from handbook
Flag : Critical study for SIDS endpoint
12.12.2002 (25) (67)

Solubility in : Water
Value : = 1000 g/l at °C
pH value :
concentration : at °C

Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Reliability : (2) valid with restrictions
29.07.2003 (46)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 87 °C
Type : closed cup
Method : other: no data
Year :
GLP : no data
Test substance :

Source : ATOFINA, Paris-La Défense, France.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Data from handbook
17.12.2002 (71)

2.8 AUTO FLAMMABILITY

Value : 300 - 302 °C at

Source : ATOFINA, Paris-La Défense, France.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Data from handbook
17.12.2002 (70)

2.9 FLAMMABILITY

Result : flammable

Source : Elf Aquitaine Lacq
Atofina Paris La Défense Cedex
23.10.1995 (123)

2.10 EXPLOSIVE PROPERTIES

Result : explosive under influence of a flame
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Explosivity limits of vapours : lel:2.6 %; uel:28.5%
Source : ATOFINA, Paris-La Défense, France.

Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
Data from handbook

12.12.2002 (126)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

Value : 2.14 - mPa s (dynamic) at 20 °C
Result :

Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
26.02.2003 (128)

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
INDIRECT PHOTOLYSIS
Sensitizer : OH
Conc. of sensitizer : 1000000 molecule/cm^3
Rate constant : = .000000000062 cm^3/(molecule*sec)
Degradation : = 50 % after 3 hour(s)
Deg. product :
Method : other (calculated)
Year :
GLP :
Test substance :

Remark : Preliminary investigations indicated that dimethylsulfone is the major reaction product (BARNES, I. et al, 1987.In: Phys. Chem. Behavior Atmos. Pollut., 327-37.)

Concentration of OH radicals = 1000000 OH/cm3 (Prin et al, 1995. Atmospheric trends and lifetime of CH3CCl3 and global OH concentration, vol. 269.)
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (1) valid without restriction
03.01.2003 (7)

Type : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight

Remark : DMSO does not contain any chromophores that absorb UV radiation above 290 nm and therefore, direct photolysis will not be significant.
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (4) not assignable
27.12.2002 (74)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C

Result : In aqueous solution, oxidation rate by OH radical, at neutral pH was 0.71E10 l/mol sec, with OH concentration in water 1E10-17 mol/l.
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
12.08.2003 (45)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C

Result : In aqueous solution, the rate of reaction of DMSO with hydroxy radicals was found to be 7.3E9 cm3/mol sec, which corresponds to a half-life range of 53 h to 732 d, assuming that OH concentration in natural waters is 0.15E-17 to 50E-17.
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex
27.12.2002 (106)

Remark : DMSO disproportionates in water to dimethyl sulfide and dimethyl sulfone. The redox reaction is catalyzed by light. DMSO is readily reduced to dimethyl sulfide by reducing agents such as Sn(II), Ti(III), Cr(II) that may be present in the environment.
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (4) not assignable
29.07.2003 (74)

3.1.3 STABILITY IN SOIL

Result : The reduction of DMSO to dimethyl sulfide (DMS) in soil was measured in a range of 47 New Zealands topsoils and humus samples.
The relationships between the rate of DMSO reduction and soil type and land use, organic C and N, the soil microbial C estimated by the substrate-induced-respiration (SIR) method, mineralization of N under anaerobic incubation and the mineralization of organic S, were investigated.

DMSO was reduced rapidly in all soils and rates ranged between 180 and 8124 ng DMS/g soil/h, with the coefficient of variance being typically <10%.

Reduction was significantly correlated with the organic carbon and N content of the 44 mineral soils (r=0.61 and 0.62 respectively), anaerobically-mineralized N (r= 0.80), microbial biomass C (r=0.81) and aerobically mineralized SO4-S (r=0.60).

The reduction of DMSO was shown to be more sensitive to the presence of Cr(VI) or As(V) than was the SIR response. The sensitivity and reproducibility of the assay make the technique potentially useful for the study of microbial activity in aggregates, rhizospheres samples and contaminated soils.
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (4) not assignable
07.02.2003 (135)

3.2.1 MONITORING DATA

Type of measurement : background concentration
Media : surface water
Concentration :
Method :

Result : DMSO is a common constituent of natural water.
A representative surface sample of seawater from the north pacific contained 0.49 ppb.
Representative samples from 3 U.S. rivers contained 0.08 to 0.11 ppb.
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

07.02.2003 (5)

Type of measurement :
Media : other: rain
Concentration :
Method :

Remark : Samples of rainwater in US contained 0.14 to 0.19 ppb (ref 1).
Samples of rain from 2 storms in the south Pacific contained 1300-2600 ng/l and 100 ng/l DMSO (ref 2).
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

07.02.2003 (4) (69)

Type of measurement :
Media : air
Concentration :
Method :

Remark : Aerosol concentration of DMSO (and other compounds) was measured with land-based stations (principally Plymouth, Devon, UK) and various shipboard stations in the North sea and North atlantic ocean.

Aerosol samples collected between July, 1985 and July, 1987 were analyzed both in terms of their back trajectories and variation with time DMSO shows seasonal cycles (abstract).
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

07.02.2003 (149)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)

Method :
Year :

Result : Level III Fugacity Model:

*Chem Name : Methane, sulfinylbis-
Molecular Wt: 78.13
Henry's LC : 1.51e-009 atm-m3/mole (Henry database)
Vapor Press : 0.622 mm Hg (Mpbpwin program)
Log Kow : -1.35 (Kowwin program)
Soil Koc : 0.0183 (calc by model)

*	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0458	4.14	1000
Water	45.9	360	1000
Soil	53.9	360	1000
Sediment	0.0766	1.44e+003	0

*	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)
Air	1.74e-012	93.3	5.57	3.11
Water	5.41e-014	1.08e+003	559	35.9
Soil	2.35e-012	1.26e+003	0	42.1
Sediment	4.5e-014	0.449	0.0186	0.015

	Advection (percent)
Air	0.186
Water	18.6
Soil	0
Sediment	0.000622

*Persistence Time: 406 hr
Reaction Time: 500 hr
Advection Time: 2.15e+003 hr
Percent Reacted: 81.2
Percent Advected: 18.8

*Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 4.14
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.027 (weeks)

*Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.06.2003 (93)

Type : adsorption
Media :
Air : % (Fugacity Model Level I)

Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	
Year	:	
Remark	:	DMSO adsorbs both chemically and physically to clay minerals. It intercalates between the layers of smectite, kaolinite, montmorillonite, dictite and halloysite. With smectite, crystallography studies indicate that a double layer of DMSO is intercalated between clay layers. With kaolin, three hydrogen bonds are formed between the kaolin hydroxyls and the DMSO oxygen.
Source	:	Atofina, Paris-le-Défense, France. Atofina Paris La Défense Cedex

29.07.2003 (6) (44) (94) (109)

Type	:	volatility
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other
Year	:	
Remark	:	The Henry's law constant at 15°C is 7.77E-9 atm cm3/mol. DMSO will therefore not volatilize from water. Its concentration would increase in time as water evaporates. At a wind speed of 1 m/sec, the volatilization rate was approximately 1.2 and 9 µg/min at -17.5 and 0 degree C, respectively.The calculated volatilization rate at zero wind velocity is 0.8 and 0.07 µg/min at 0 and -20 degree C, respectively.
Source	:	Atofina, Paris-le-Défense, France. Atofina Paris La Défense Cedex

29.07.2003 (73)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/l related to Test substance related to
Contact time	:	
Degradation	:	= 3.1 (±) % after 14 day(s)
Result	:	other

Deg. product :
Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 1981
GLP : no data
Test substance : no data

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.06.2003 (12)

Type : aerobic
Inoculum : other: see remark
Concentration : 100 µg/l related to
related to
Contact time : 24 hour(s)
Degradation : (±) % after
Result : other: see remark
Deg. product :
Method : other: see remark
Year : 1978
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : To 10 ml TYEG medium, sterilized in a 40 ml serum vial, sterile DMSO was added to a final concentration of 100 µg/ml.

After the medium had been inoculated, the vials were sealed with teflon-coated rubber stoppers.

For anaerobic incubations, the headspace was gassed with sterile nitrogen. Cultures were incubated at 30°C for 24 h. The headspace was then sampled and analyzed for DMS by GC.

Remark : DMSO was reduced to DMS by 15 different microorganisms including prokaryotes, eukaryotes, aerobes and anaerobes.

Micoorganisms	% DMSO reduced to DMS
- Escherichia coli	18.0
- Salmonella thyphimurium	10.5
- Klebsiella pneumoniae	37.0
- Proteus vulgaris	24.0
- Providencia alcalifaciens	26.0
- Pseudomonas aeruginosa	27.0
- Staphylococcus aureus	0.5
- Streptococcus faecalis	0.2
- Bacillus subtilis	17.0
- Bacillus cereus	0.5
- Clostridium butyricum	0.1
- Arthrobacter sp.	5.0
- Desulfovibrio sp.	1.1
- Aspergillus niger	3.0
- Saccharomyces cerevisiae	4.5

Dimethyl sulfone was not reduced by any of the microorganisms.
Activity was greater in anaerobically grown cells than in those grown aerobically.

Source : Elf Aquitaine Lacq
ECB - Existing Chemicals Ispra (VA)
Maslansky GeoEnvironmental, Inc. Prescott, AZ

Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
12.08.2003 (159)

Type : aerobic
Inoculum : activated sludge, adapted
Concentration : 200 mg/l related to Test substance
related to
Contact time :
Degradation : (±) % after
Result : under test conditions no biodegradation observed
Deg. product :
Method : other
Year :
GLP : no data
Test substance : no data

Method : The test apparatus was a 3.0 l cylindrical acrylic container, operated in a sequential batch manner.
The air flow rate and water temperature could be controlled.
The water samples were adjusted so that their concentration was 100-200 mg/l in terms of COD(Mn) or about 100 mg/l in term of concentration of test substance.
The temperature was 25-30°C and pH was adjusted to neutral.

The operational procedure was as follows: 2.0 l of the sample water was added to 0.5 l of activated sludge and the aeration of the mixed liquor was started.
After 23h aeration, and 1 hour of sedimentation, 2.0 l of the supernatant solution was replaced by the sample water (fill and draw method).

After one or several days of fill and draw operation (depending on the substance) to acclimatize the sludge to the test water, the water in the container was sampled during aeration at 0 hours (the initial concentration) and 24 h later (the final concentration) for analysis.
Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
12.08.2003 (102)

Type : aerobic
Inoculum :

Remark : In batch system, with activated sludge as inoculum, degradation of DMSO was < 20%.
Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Reliability : (4) not assignable
07.02.2003 (157)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Species : Cyprinus carpio (Fish, fresh water)

Exposure period	:	42 day(s) at 25 °C
Concentration	:	1 mg/l
BCF	:	< .4
Elimination	:	no data
Method	:	OECD Guide-line 305 C "Bioaccumulation: Test for the Degree of Bioconcentration in Fish"
Year	:	1981
GLP	:	no data
Test substance	:	no data
Remark	:	With 0.1 mg/l DMSO, BCF < 4. Exposure method : Continuous flow system Analytical method : Gas chromatography
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

27.12.2002 (13)

3.8 ADDITIONAL REMARKS

Remark	:	Formaldehyde is produced when DMSO reacts with OH radicals. OH radicals are produced by oxidation of xanthine by xanthine oxydase. With 3.3 mM DMSO, there was 10.88+-4.25 mmol/30 min formaldehyde produced. With 33 mM DMSO, there was 12.12+-3.64 mmol/30 min formaldehyde produced.
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex

03.06.2003 (87)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : flow through
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : g/l
LC50 : = 34
Limit test :
Analytical monitoring : yes
Method : other
Year :
GLP : no data
Test substance : other TS: > 99%

Result : Toxicant stock : 59.1 g/l
Fish were exposed to 0%, 20%, 40%, 60%, 80% and 100% of the stock solution.

DMSO Concentrations (g/l)

		A	B	C	D	E
Nominal	0	11.4	22.8	34.1	45.5	56.9
Measured		8.33	13.8	23.6	26.9	55.6
		9.58	21.4	28.5	46.1	56.3
		7.30	22.7	28.3	44.6	56.7
		9.12	23.4	27.8	46.5	60.1
		10.2	20.3	27.8	45.2	54.3
Average		8.91	20.3	27.2	41.9	56.6

% recovery 99.3 (Standard deviation : 7.3) (number of samples : N=8)

Method of chemical analysis : Gas-liquid chromatography

Number of fish : 10

MORTALITIES

C	A	B	C	D	E
T0			0	0	0
24			0	10	10
48			0	10	10
72			0	10	10
96			0	10	10

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Test condition : Adult fatheads minnows were held at 25°C in flowing water with a controlled photoperiod of 16 h light.
They were fed frozen adult brine shrimp (Artemia sp.).

Age: 31 days, ,
Mean length: 15.8 mm (SD : 3.259)
Mean weigh: 0.062 g (SD : 0.0493)

Temperature: 24.9°C
Dissolved oxygen: 7.0 mg/l
Hardness: 44.3 mg/l CaCO3
Alkalinity: 46.2 mg/l CaCO3

Tank volume: 0.25 l
pH: 7

Test substance : DMSO purity >99%
Reliability : (1) valid without restriction
Flag : Material Safety Dataset, Critical study for SIDS endpoint
12.08.2003 (65)

Type : other: static (Renewal of test water at 24 hrs) or semi-static (Renewal of test water at every 8-16hrs)
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : g/l
LC50 : = 33
Limit test :
Analytical monitoring : no data
Method : other: in accordance with Japanese Industrial Standard (JIS K 0102-1986-71) titled " Testing methods for industrial wastewater"
Year : 1986
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Test condition : - Conditions for fish keeping :
At reception, fishes showing abnormal signs were removed.
Then fishes were reared according to flow through system for 2-3 weeks after external disinfection.

- Condition of acclimatation :
Fishes were reared in an acclimatization tank according to flow through system at temperature of 25+-2 °C for about 28 days.
During the period, abnormal fishes were removed.

- Dilution water for the test
Origin : underground water
Water temperature, pH and dissolved oxygen were continuously measured.
Total hardness, evaporated residue, chemical oxygen demand, chloride ion, ammoniacal nitrogen, harmful substances such as organic phosphorus compounds, cyanide ion and heavy metal etc.., were analyzed regularly once a six months.
The quality of the dilution water used for the test was confirmed to meet the ministerial ordinance of the Ministry of Health and Welfare (August 31, 1978) in total hardness and evaporated residue.

- Test conditions :
Test tank : round glass vessel
Volume of test water : 4l/level
Temperature of test water : 25+-2°C
Number of fish : 10 fishes/level

-The 48h LC50 value was estimated by Doudoroff method or Probit method
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.07.2003 (14)

Type : Static
Species : Oncorhynchus mykiss (Fish, fresh water)

Exposure period	:	96 hour(s)
Unit	:	g/l
LC50	:	= 33 - 37
Limit test	:	
Analytical monitoring	:	No
Method	:	Other
Year	:	1975
GLP	:	no data
Test substance	:	no data
Method	:	Committee on methods for toxicity tests with aquatic organisms.1975.Methods for acute toxicity tests with fish, macroinvertebrates and amphibians.US Environmental Protection Agency, Ecol. Res. Serv., EPA-660/3-75-009.61 pp.
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Test condition	:	- Life stage: 0.7 g - Temperature: 12°C - Hardness: 40 to 50 mg/l CaCO3 - Alkalinity: 30 to 35 mg/l CaCO3 - pH: 7.2 to 7.5 Test water (dilution water) was reconstituted from deionized water of at least 10E6 ohms resistivity by the addition of the appropriate reagent grade chemicals. Fish were acclimated to dilution water by gradually changing the water in acclimatation tanks from 100% well water to 100% reconstituted water over a 1 to 3 day period at the desired testing temperature. Temperature of test solutions was maintained within +/ -1°C. Fingerling fish weighing 0.2 to 1.5 g were tested at each concentration. At least 10 organisms were exposed to each concentration in definitive test.At least 6 concentrations were used per toxicity test.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

03.06.2003 (83)

Type	:	Static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	g/l
LC50	:	> 40
Limit test	:	
Analytical monitoring	:	No
Method	:	Other
Year	:	1975
GLP	:	no data
Test substance	:	no data
Method	:	Committee on methods for toxicity tests with aquatic organisms.1975.Methods for acute toxicity tests with fish, macroinvertebrates and amphibians.US Environmental Protection Agency, Ecol. Res. Serv., EPA-660/3-75-009.61 pp.
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Test condition	:	- Life stage: 1.0 g - Temperature: 24°C - Hardness: 40 to 50 mg/l CaCO3

- Alkalinity: 30 to 35 mg/l CaCO3
- pH: 7.2 to 7.5

Test water (dilution water) was reconstituted from deionized water of at least 10E6 ohms resistivity by the addition of the appropriate reagent grade chemicals.

Fish were acclimated to dilution water by gradually changing the water in acclimatation tanks from 100% well water to 100% reconstituted water over a 1 to 3 day period at the desired testing temperature.

Temperature of test solutions was maintained within +-1°C. Fingerling fish weighing 0.2 to 1.5 g were tested at each concentration.
At least 10 organisms were exposed to each concentration in definitive test.At least 6 concentrations were used per toxicity test.

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.07.2003 (82)

Type : static
Species : other: several species
Exposure period :
Unit : g/l
Limit test :
Analytical monitoring : No
Method : other: no data
Year :
GLP : No
Test substance : other TS: 90% in water

Remark : After preliminary assay carried out with yellow perch , bioassays were conducted in a 5-gallon glass jars each containing 15 l of reconstituted deionized water and ten fish.
Each test included 5 to 9 concentrations of chemical and 50 to 90 test fish plus 10 fish for control.

Various water qualities were obtained by adding selected concentrations were obtained by adding selected concentrations of reconstituting salts to deionized water:

	pH	total hardness as ppm CaCO3	total alkalinity as ppm CaCO3
- Soft	6.4-6.8	10-13	10-13
- Medium	7.2-7.6	40-48	30-35
- Hard	7.6-8.0	160-180	110-120

Survival and mortality were recorded at 24, 48 and 96 h.The data were analyzed by plotting concentration versus mortality on log (probability) graph pa

Result : Toxicity of 90% DMSO to nine species of fish at 12°C

LC50 (g/l)	24h	48h	96h
- (Salvenilus fontinales)			
Brook trout	54.5	46.0	36.5
95% CI	(50.9-58.3)	(42.2-50.1)	(33.2-40.2)

- (Salvenilus namaycush)

Lake trout	47.8	38.2	37.3
95% CI	(42.3-54.0)	(35.4-41.3)	(35.2-39.5)

- (Oncorhynchus mykis)

Rainbow trout	53.0	41.7	32.3
95% CI	(48.6-57-8)	(39.3-44.2)	(30.2-34.6)

- (Cyprinus carpio)

Carp	44.0	44.0	41.7
95% CI	(39.3-49.3)	(39.3-49.3)	(36.3-48.0)

- (Ictalurus melas)

Black bullhead	42.5	39.2	36.5
95% CI	(37.9-47.6)	(35.3-43.5)	(33.8-39.4)

- (Ictalurus punctatus)

Channel catfish	39.0	34.5	32.5
95% CI	(36.1-42.1)	(31.7-37.6)	(29.8-35.4)

- (Lepomis cyanellus)

Green sunfish	65.0	52.5	43.0
95% CI	(61.3-68.9)	(47.7-57.8)	(35.8-51.6)

- (Lepomis macrochirus)

Bluegill	72.0	56.0	33.5
95% CI	(63.2-82.1)	(51.9-60.5)	(29.9-37.5)

- (Perca flavascens)

Yellow perch	65.0	57.0	37.0
95% CI	(61.3-68.9)	(52.3-62.1)	(33.9-40.3)

Changes in water quality at 12° C had no or little effect upon the toxicity of DMSO

Water quality	LC50, 96 h (g/l)
Soft	33.5 (30.7-36.5)
Medium	32.3 (30.2-34.6)
Hard	38.0 (35.0-40.3)

Increases in temperature at medium hardness cause a definitive increase in the toxicity of rainbow trout

°C	LC50, 96 h (g/l)
7	41.5 (37.7-45.6)
12	32.3 (30.2-34.6)
17	27.7 (25.0-30.7)

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

29.07.2003 (151)

Remark : The toxic and cryoprotective effects of 10% DMSO concentration were studied in early stages of loach embryo development (stage 2(8 blastomeres) to stages 27-33

(organogenesis)).

Embryos at stages 22-28 of development were most resistant to the toxic effects of DMSO.
Maximum cryoprotection was observed at stages 25-33.
The number of embryos which did not survive increased with decreasing temperature from 0 to -10 degree C.
The number of embryos with developmental defects was greatest at -2 degree C.
At lower temperatures, embryos died rather than developed abnormally.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Reliability : (3) invalid
07.02.2003 (143)

Type : other: see remark
Species : Oncorhynchus sp.
Exposure period :
Unit :
Limit test :
Analytical monitoring : no data
Method : other
Year : 1968
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : ACUTE AND CHRONIC TOXICITY

- Intraperitoneal injection studies
The acute toxicity (g DMSO/kg body weight) of DMSO to chinook salmon (Oncorhynchus tshawytscha): LD50 = 12.0, sockeye salmon (O. nerka): LD50 = 13.0, coho salmon (O. kisutch): LD50 = 16.0 and rainbow trout (Salmo gardneri): LD50 = 17.0 was determinated by intraperitoneal injections of aqueous solutions of DMSO.
Fish usually died within 24 h; however, a few died between 24 and 48 hours. Symptoms of toxicity were intermittent spasms and disorientation of swimming shortly before expiring.
In the preliminary chronic study, moderate hematologic changes were observed in fish receiving daily injections of 9.0 - 31 g per kg of body weight (30-100% DMSO) and consisted in slight pycnosis of red blood cell nuclei and moderate degeneration of white blood cells.
Average death rates for this group was : 31 g/kg (100%), 4 h; 12 g/kg (50%), 33 h; 10 g/kg (40%), 90h and 9.0 g/kg (30%), 130 h.
No mortality was observed in fish injected with 0.9 g/kg.
Histologic alterations noted in fish injected with 31 g/kg were confined to liver, kidney, spleen and pancreas.

- Immersion study
Median tolerance limit (TLm) in yearling coho salmon was:
TLm, 24h = 7.2%
TLm, 48h = 5.5%
TLm, 72h = 4.9%
TLm, 96h = 4.6%
LET50 for coho salmon was determined over a range of 2.0-16.0%.
Groups of fish exposed to DMSO concentrations of 0.01, 0.1 and 2.0% for a period of 100 days; there was no mortality

and all groups except fish exposed to 2.0% level gained weight.
Morphologic changes were observed in blood cells from fish exposed to 8, 12 and 16% DMSO and consisted of slight to moderate degeneration of erythrocytes and leukocytes.
Tissues of fish subjected to 4% DMSO revealed moderate to severe damage to gills and kidney.
Exposure to 8 and 16% produced similar changes in gills and kidney.
Fish immerged in 16% DMSO revealed marked engorgement and dilation of brain and menigeal blood vessels, engorgement of cerebral capillaries, and cerebral edema.

- Oral studies
No mortality was observed when DMSO (0.01% to 20% v/w) was fed as a dietary ingredient.
Fish ingesting DMSO displayed a dose-dependent decrease in diet consumption and body weight gain.
Hematologic differences were noted in fish receiving 15 and 18% DMSO in their diets.
Histopatholic examinations were conducted on fish fed 6, 12, and 18% DMSO.
Lesions observed in the 12% group were confined to gill lamellae and consisted of moderate edema and moderate to severe epithelial cell hypertrophy.
Similar, more pronounced changes were observed fish receiving 18% DMSO.

The injection, immersion and ingestion experiments showed a safe level for yearling coho salmon of 2.8 g of DMSO /kg body weight /day for 28 days, 1% v/v per 100 days and 1% v/w for 16 weeks, respectively.
These fish would tolerate higher concentrations of DMSO for a shorter period of time and recover rapidly when removed from DMSO.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Reliability : (3) invalid
12.08.2003 (11)

Type : other
Species : Oncorhynchus mykiss (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : g/l
LC0 : = 30.8
LC50 : = 38
Limit test :
Analytical monitoring : no data
Method : other: no data
Year :
GLP : no data
Test substance : no data

Remark : Life stage: fingerling
Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Test condition : Temperature: 12°C
Reliability : (4) not assignable
27.12.2002 (10)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	= 7000
Analytical monitoring	:	no
Method	:	ISO 6341 15 "Water quality - Determination of the inhibition of the mobility of Daphnia magna Straus (Cladocera, Crustacea)"
Year	:	
GLP	:	no
Test substance	:	no data
Remark	:	Control performed on potassium bichromate (EC50, 24h = 1.2 mg/l).
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Reliability	:	(4) not assignable
Flag	:	Critical study for SIDS endpoint

27.12.2002 (122)

Type	:	
Species	:	Daphnia pulex (Crustacea)
Exposure period	:	18 hour(s)
Unit	:	mg/l
EC50	:	= 22300 - 27100
Analytical monitoring	:	no
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	no data
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Test condition	:	Method reported by: STEPHAN, C.E.: Methods for acute toxicity tests with fish, macroinvertebrates and amphibians.U.S. Environmental Protection Agency, Report N° EPA-660/3-75-009, Covallis, OR, 1975. Bioassay had a duration of 18 h, which allowed ample time for the preparation of samples and calculation and reporting of results within a 24 h period. Temperature : 23+-1°C Number of organisms : 10
Reliability	:	(4) not assignable

07.02.2003 (16)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	
Unit	:	g/l
EC50	:	= 58.2
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Reliability	:	(4) not assignable

27.12.2002 (43)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	g/l
EC50	:	= 19.25
Analytical monitoring	:	no data
Method	:	other: Norme AFNOR T 90-301
Year	:	1974
GLP	:	no data
Test substance	:	no data
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Test condition	:	Temperature : 20+-1°C
Reliability	:	(4) not assignable

27.12.2002 (54)

Type	:	
Species	:	Artemia salina (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC	:	= 1300 - 13000
Analytical monitoring	:	no
Remark	:	Life stage of tested organism: nauplii I The assay is based on disturbance of elongation development (relative to controls raised at the same time) from 24 h to 48 h in animals cultured in medium containing a presumptive teratogen. A sample of 50 insulted animals is measured and their average length is compared with that of control animals. A statistically significant difference between the length averages is taken as indicative of teratogenesis. It was considered a significant difference to represent 20% or more of the expected growth increment of the controls from 24 to 48 h. DMSO presented no teratogenicity in concentrations ranging from 0.13% to 1.3%.
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex

07.02.2003 (86)

Type	:	
Species	:	Artemia salina (Crustacea)
Exposure period	:	
Unit	:	g/l
EC50	:	= 68.6
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex

03.06.2003 (42)

Type	:	
Species	:	Artemia salina (Crustacea)
Exposure period	:	
Unit	:	
Remark	:	Brine shrimp was exposed to DMSO at various stages of its life cycle. Toxicity was not related to developmental stage for DMSO.

(abstract).

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

03.06.2003 (8)

Type :
Species : other aquatic arthropod: Culex pipiens molestus (larvae)
Exposure period :
Unit : g/l
EC50 : = 23.2

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

03.06.2003 (41)

Type :
Species : other aquatic arthropod: Culex restuans
Exposure period : 18 hour(s)
Unit : g/l
EC50 : = 25.9 - 30.7
Analytical monitoring : no
Method : other
Year : 1975
GLP : no
Test substance :

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Test condition : Method reported by:
STEPHAN, C.E.: Methods for acute toxicity tests with fish, macroinvertebrates and amphibians.U.S. Environmental Protection Agency, Report N° EPA-660/3-75-009, Covallis, OR,1975.
Bioassy had a duration of 18 h, which allowed ample time for the preparation of samples and calculation and reporting of results within a 24 h period.

12.08.2003 (18)

Type :
Species : other aquatic crustacea: Hyalella azteca
Exposure period : 18 hour(s)
Unit : mg/l
EC50 : = 31900 - 58000
Analytical monitoring : no
Method : other
Year : 1975
GLP : no
Test substance :

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Test condition : Method reported by:
STEPHAN, C.E.: Methods for acute toxicity tests with fish, macroinvertebrates and amphibians.U.S. Environmental Protection Agency, Report N° EPA-660/3-75-009, Covallis, OR,1975.
Bioassy had a duration of 18 h, which allowed ample time for the preparation of samples and calculation and reporting of results within a 24 h period.

12.08.2003 (15)

Type :
Species : other aquatic crustacea: Palaemonetes kadiakensis
Exposure period : 18 hour(s)

Unit	:	mg/l
EC50	:	= 22100 - 45000
Analytical monitoring	:	no
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Test condition	:	Method reported by: STEPHAN, C.E.: Methods for acute toxicity tests with fish, macroinvertebrates and amphibians.U.S. Environmental Protection Agency, Report N° PA-660/3-75-009, Covallis, OR,1975. Bioassy had a duration of 18 h, which allowed ample time for the preparation of samples and calculation and reporting of results within a 24 h period.

12.08.2003 (17)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Chlorella pyrenoidosa (Algae)
Endpoint	:	growth rate
Exposure period	:	14 day(s)
Unit	:	
Limit test	:	
Analytical monitoring	:	no
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data
Remark	:	Flasks were incubated at 25+-1°C and a light intensity of 7 klux on a 12 hour light-dark cycle. Growth was monitored by following the increase of optical density over time for 10 to 14 days (precise duration not specified). The solvent was assayed at 10 concentrations ranging from 0.1% to 4.0% (v/v) or 1 to 40 g/l. EC50 value (% v/v), calculated using linear regression analysis (percent inhibition versus solvent concentration), was 2.01 (95% CI : 1.76-2.26).
Source	:	ATOFINA, PARIS-LA-DEFENSE, FRANCE. Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions
Flag	:	Material Safety Dataset

03.06.2003 (136)

Species	:	other algae: Anabaena sp. and Nostoc sp.
Endpoint	:	growth rate
Exposure period	:	
Unit	:	mg/l
Limit test	:	
Analytical monitoring	:	no
Method	:	other
Year	:	
GLP	:	no data

Test substance : no data

Remark : Five species of blue-green algae were used as test cultures :

- Anabaena sp.
- Anabaena cylindrica .
- Anabaena variabilis
- Anabaena inaequalis
- Nostoc sp.

Flasks were incubated at 25+-1°C and a light intensity of 7 klux on a 12 hour light-dark cycle.

Growth was monitored by following the increase of optical density over time for 10 to 14 days.

The solvent was assayed at 10 concentrations ranging from 0.1% to 6.0% (1 to 60 g/l).

EC50 value was calculated using linear regression analysis (percent inhibition versus solvent concentration).

Results

	EC50 %(v/v)	95% CI
- Anabaena variabilis :	3.57	(2.32-4.82)
- " inaequalis :	1.71	(1.24-2.18)
- " cylindrica :	0.84	(0.25-1.43)
- Anabaena sp. :	0.39	(0.12-0.66)
- Nostoc sp. :	4.02	(3.64-4.40)

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

Flag : Material Safety Dataset

03.06.2003 (137)

Species : Dunaliella bioculata (Algae)
Endpoint : growth rate
Exposure period : 48 hour(s)
Unit : g/l
EC0 : = .5
EC12 : = 10
Limit test :
Analytical monitoring : no
Method : other
Year :
GLP : no
Test substance :

Remark : EC4, 48h = 1 g/l (96% growth)

This indicates that there is 4% of growth inhibition.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Test condition : Bacteria-free algae were maintained on agar plates.

200 ml medium were inoculated with D. bioculata from agar plates and incubated at 24°C under continuous light.
Air containing 5% CO2 was bubbled through.At an optical density of 0.6 at 600 nm (about 4 days), 60 - 100 ml of the algae could be transferred to 600 ml of the main culture.

The main culture was diluted to an optical density of 0.6+-0.05 (at 600 nm) with fresh medium, when it was in the logarithmic phase (optical density below 2.0).

Shaking flasks were used in screening assays.

19 ml of a culture with an optical density of 0.6+-0.05 and 1 ml of a solution containing a chemical were shaken at 120 rpm at 24°C under continuous light.
Effects of chemical on growth are compared with the control, where the optical density increased from 0.6 to 0.85 within 48 h.

Reliability : (3) invalid
10.02.2003 (53)

Species : other algae: Chlamydomonas eugametos
Endpoint : growth rate
Exposure period : 48 hour(s)
Unit : g/l
EC63 : = 25
Limit test :
Analytical monitoring : no
Method : other
Year :
GLP : no
Test substance : no data

Remark : Effect concentration :calculated by Aquire staff based on data in paper.
Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Test condition : Temperature : 25°C
pH : 6.7
Reliability : (3) invalid
27.12.2002 (72)

Species :
Endpoint : growth rate
Exposure period :
Unit :
Limit test :
Analytical monitoring : no
Method : other
Year :
GLP : no
Test substance : no data

Method : Flasks were rotated at 130 rpm on a rotary shaker at 24°C under fluorescent lighting of 310 fc.

Incubation period varied from 2 to 10 days.

Growth was determined in a Bausch and Lomb Spectronic 20 spectrophotometer at a % transmittance of 450 nm.

Type of water not reported.
Remark : -Coelastrum microporum Naeg. (algae)
-Bracteacoccus cinnibarinus
-Anacystis nidulans (bacteria)
-Serratia marcescens (bacteia)
Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.

Atofina Paris La Défense Cedex
Reliability : (4) not assignable
07.02.2003

Species : Skeletonema costatum (Algae)
Endpoint : growth rate
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : = 12350 - 25500
Limit test :
Analytical monitoring : no data
Method : other
Year :
GLP : no
Test substance : no data

Remark : Saltwater algae.
Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
Reliability : (4) not assignable
07.02.2003 (33)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : Photobacterium phosphoreum (Bacteria)
Exposure period : 5 minute(s)
Unit : mg/l
EC50 : = 77
Analytical monitoring : no
Method : other
Year :
GLP : no
Test substance :

Remark : Test performed at 15°C with a photometer MICROTOX.

The EC50 value was compared with EC50, 24h to Daphnia magna, a test performed by : IRCHA, les produits chimiques dans l'environnement, Paris, 1981.It was found for Daphnia: 19250 mg/l.
Microtox test was more sensible than acute toxicity test to daphnia.
Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex
07.02.2003 (55)

Type : aquatic
Species : Tetrahymena pyriformis (Protozoa)
Exposure period : 24 hour(s)
Unit : g/l
EC50 : = 32
Analytical monitoring : no
Method : other
Year :
GLP : no data
Test substance :

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Test condition : The method was carried out under sterile conditions
Tetrahymena pyriformis was precultured at 30°C for 24h.
Two different counting methods were used.One used a microscope, the other a Coulter counter.

07.02.2003 (156)

Type : aquatic
Species : other protozoa: Vorticella nebulifera
Exposure period : 12 hour(s)
Unit : g/l
EC : = 35

Remark : Immersion of healthy populations of V. nebulifera resulted in lethal damage to the outermost pellicular membrane and electron microscopy revealed electron-donor in the pellicle.

similar exposures to 10-32.5 g/l DMSO were not fatal if the organisms were washed with isotonic salt solution at the end of the immer sion period.
Treatment with these lower concentrations did not interfere with subsequent reproduction.
RANGANATHAN, V.S., 1976.Effects of dimethyl sulfoxide on the pellicle of the peritrich ciliate Vorticella nebulifera.
Trans. Am. Microsc. Soc., 95(3), 394-399.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

07.02.2003

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

Species : other avian
Endpoint : mortality
Exposure period : 18 hour(s)
Unit : mg/kg bw
LD50 : = 100

Remark : Repellency value (R50)= 1.0 %
Repellency-toxicity index (hazard factor)=0.769 , indicating that DMSO has a possible potential for acute oral poisoning.
In the same studies, for starling (Sturnus vulgaris),

LD50= 100 mg/kg.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

Test condition : Method: wild-trapped birds were preconditionned to captivity for 2 to 6 weeks and were usually dosed by gavage with solutions or suspensions of the test chemical in propylene glycol, according to methods described by DeCino et al (1966), Schafer (1972) and Schafer et al (1967).

LD50 values were calculated by the method of Thompson (1948), Thompson and Weil (1952) and Weil (1952). Repellency tests were conducted by the methods of starr et al (1964) and Schafer and Brunton (1971), and R50's were calculated either by the method of Litchfield and Wilconxin (1949) or Thompson and Weil (1952).

Bird species: Agelaius phoeniceus (Red-winged blackbird).

22.07.2003 (127)

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

Type : aquatic
Deg. product :

Remark : The toxic and cryoprotective effects of 10% DMSO concentration were studied in early stages of loach embryo development (stage 2(8 blastomeres) to stages 27-33 (organogenesis)).Embryos at stages 22-28 of development were most resistant to the toxic effects of DMSO.

Maximum cryoprotection was observed at stages 25-33.The number of embryos which did not survive increased with decreasing temperature from 0 to -10 degree C.The number of embryos with developmental defects was greatest at -2 degree C.At lower temperatures, embryos died rather than developed abnormally.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

07.02.2003 (143)

Type : aquatic
Deg. product :

Remark : Intact developing embryos of the zebrafish Brachydanio rerio were exposed to (14C)DMSO (1 M in fish ringer's solution) to assess the degree of permeation of this cryoprotectant.

DMSO entered the embryo, reaching only approx. 2.5% of the expected equilibrium level after 2h at room temperature.

To identify the barrier to permeation, dechorionated embryos were similarly exposed to isotopic DMSO.Permeation increased several fold, indicating that the chorion retards the free exchange of solute.

Embryos were unaffected by exposure to 1M DMSO at 23 degree C.

The number of embryos hatching after 1h exposure to DMSO at varying concentrations was decreased at 1.5 and 2 M.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

07.02.2003 (116)

4.9 ADDITIONAL REMARKS

Remark : Species: amphibians

Newts were collected during the summer and spring, acclimated for 10 days at 10°C, weighed, treated with DMSO and maintained in an unfed state which simulated winter conditions.

Intraperitoneal injections of 15 g DMSO/kg or immersion in 2% DMSO were determined to be lethal threshold doses for newts. Death was rapid.

In addition to a transient increase in the body weight of the DMSO-treated animals, other changes were observed:
- a reduction in respiration to 70% that of the controls
- an increase in the weights of spleen (by day 1, the average spleen weight was over twice that of the controls), liver (33% increase after 24 h), and abdominal fat (150% increase after 20 days).

Lethality was attributed primarily to irreversible changes in the permeability of the skin, causing a water imbalance, hyperhydration and death.The reduced respiratory rate increased the mortality rate.

Source : ATOFINA, PARIS-LA-DEFENSE, FRANCE.
Atofina Paris La Défense Cedex

03.06.2003 (89)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species : monkey
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle : water
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The absorption and excretion of DMSO were studied in Rhesus monkeys during and after 14 days oral administration of 3 g DMSO/kg. DMSO and its major metabolite, dimethylsulfone (DMSO2), were measured in serum, urine and feces by gas-liquid chromatography.

Result : Serum Concentrations of DMSO and DMSO2
To determine its absorption and maximal blood level, DMSO was measured in serum of Rhesus monkeys at 1, 2, 4, 6, 8 and 24 hrs after the initial oral dose. An average peak serum concentration of 2.3 mg/ml was observed after about 4 hrs which declined relatively rapidly to about 0.95 mg/ml after 24 hrs (Fig. 1). The decline in serum DMSO was linear on semilogarithmic coordinates, i.e. a constant fraction was eliminated in each interval time. Its half-life of 16 hrs was found by measuring the time required for a given serum concentration to decline by one-half. Its elimination rate constant Ke=0.693/16, or about 4% per hr.

With continued daily oral administration, serum DMSO rose slightly from 0.95 to 1.1 mg/ml on day 2 and then reached a steady state concentration of about 0.9 mg/ml after 4 days (Figure 2). The increase of serum DMSO on day 2 was not statistically significant from the steady state concentration reached on day 4. After oral DMSO was stopped, serum DMSO declined rapidly and was not detected after 72 hrs.

DMSO2 became detectable in serum after about 2 hrs, rose slowly and reached about 0.18 mg/ml at 24 hrs (Figure 1). With continued DMSO treatment, DMSO2 attained a steady state concentration of 0.34 mpg/ml after 4 days (Figure 2). When oral DMSO was stopped after 14 days, the mean DMSO2 serum

concentration declined slowly over the next 96 hrs and trace amounts were detected at 120 hrs. The decline in serum DMSO2 was approximately linear on semilogarithmic coordinates. Its half-life was calculated to be about 38 hrs and its elimination rate constant equaled 0.018, or about 2% per hr.

Urine Concentrations of DMSO and DMSO2
The average total urinary excretion of DMSO and DMSO2 in the monkeys is shown in Figure 3. Urinary excretion of DMSO increased rapidly, reached a steady state level of approximately 9 gms/day after 2 days. The increase in DMSO excretion at 5 days reflected an increased urine volume on that day. DMSO disappeared rapidly from urine after treatment ended and only trace amounts were detected after 72 hrs. About 128 gms, or 60% of the ingested DMSO was excreted in the urine unchanged.

Urinary excretion of DMSO2 increased slowly and reached a maximum of about 3 gms/day after 5 days of DMSO administration (Figure 3). Excretion remained between 2-3 gms/day during the remainder of oral DMSO. Once DMSO treatment stopped, urinary DMSO2 declined slowly over the next 5 days.
Approximately 33 gms, or about 16% of the ingested DMSO was excreted in urine as DMSO2.

Elimination of DMSO in Feces
All fecal samples were collected and stored at 4°C for several weeks prior to analysis by gas-liquid chromatography. Although freshly collected fecal samples smelled of DMSO, no DMSO or DMSO2 was detected when they were analyzed two weeks later. Because of this, we considered the possibility that gut bacteria had degraded the compounds during storage. In an attempt to determine this, DMSO was added to a 5 ml suspension of 1.89 gms of control monkey feces at a final concentration of 1000 uµ/ml. The mixture was incubated at 37°C and at 1, 2, 4, 6 and 8 hrs small aliquots were taken for analysis. The amount of DMSO in the incubation mixture decreased with time. After 8 hrs none could be detected. DMSO2 was not detected at any time during the incubations. The slope of the line representing the loss of DMSO with time was calculated to be 0.64 for DMSO degraded per hr. Since the incubation mixture contained 1.89 gms of feces, approximately 0.34 mg of DMSO was degraded per hr per gm of feces. Based upon an average excretion of about 60 gms of feces per day, we estimated that gut bacteria may be responsible for degrading 450-500 mg of DMSO per day, or about 7 gms of DMSO over the treatment period. This would represent about 3% of the total DMSO ingested.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Attached document : Layman figure 1.bmp
Layman figure 2.bmp
Layman figure 3.bmp

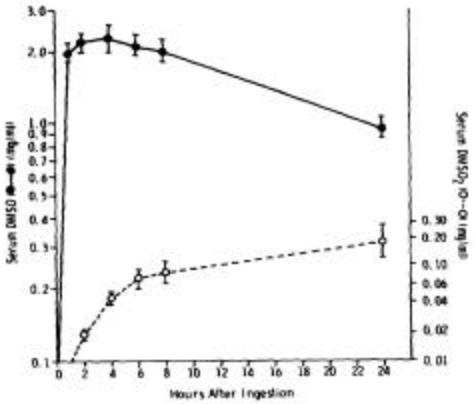

FIG. 1

Serum DMSO and $DMSO_2$ in Monkeys After a Single Oral Dose of 3 gms DMSO Per kg Body Weight.

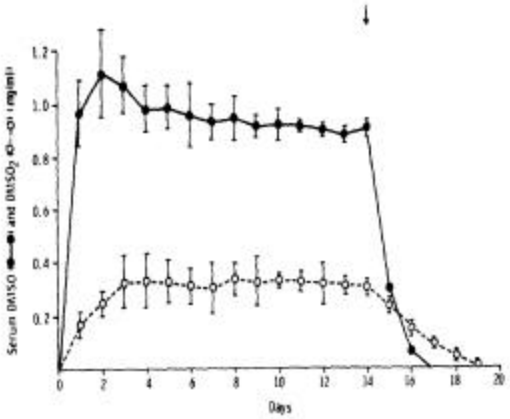

FIG. 2

Serum DMSO and $DMSO_2$ in Monkeys Given Daily Oral Doses of 3 gms DMSO Per kg Body Weight for 14 Days. Arrow Indicates Last Dose.

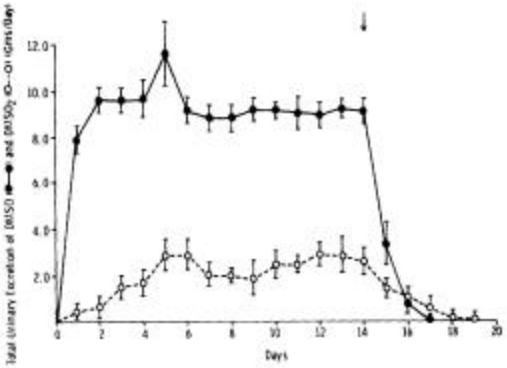

FIG. 3

Urinary Excretion of DMSO and $DMSO_2$ in Monkeys Given Daily 3 gms DMSO Per kg Body Weight for 14 Days. Arrow Indicates Last Dose.

Reliability : (2) valid with restrictions
12.08.2003

In Vitro/in vivo : In vivo
Type : Toxicokinetics
Species :

Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Absorption, distribution and metabolism of DMSO have been studied in rats, rabbits and guinea pigs using S35-labeled DMSO. Male Sprague-Dawley rats (160-210 g) received 0.55 g/kg (0.5-11 µC) of S35-DMSO orally, dermally or intraperitoneally. The animals were sacrificed at various times, and as much blood as possible was removed from the heart by intracardiac puncture. Tissues were removed, blotted, weighed and homogenized.
Male New Zealand white rabbits kept in stocks received 0.55 g/kg (approximately 7 µC) of S35-DMSO dermally. The animals were bled from an ear vein at various times, killed by cervical dislocation and bled. Tissues were removed and homogenized. Aqueous humor was removed. Urine and feces were collected separately from rats and rabbits and guinea pigs receiving DMSO. Rats were placed in all-glass metabolism cages to collect expired air. Biological samples were analysed by paper, thin layer or gas chromatography.

Result : Absorption of DMSO and its half-life in plasma:
Rats received S35-DMSO (0.55 g/kg, approximately 0.5 µC) dermally, orally and intraperitoneally and were killed at various times and the plasma assayed for total radioactivity. There were appreciable concentrations of radioactivity in the plasma 0.5 hr after dosing by all routes. The concentration was highest at 2 hr after dermal administration, at which time the level was nearly the same as the maximum attained at 0.5 to 1 hr after either oral or intraperitoneal administration. The levels thereafter declined, with an average half-life of approximately 6 hr. After 24 hr, the levels had declined to about 5 to 10% of the peak concentration.
The rate of passage of dermally applied S35-DMSO through the skin was also estimated in rats and rabbits. Eight rats were dosed dermally with 0.5 5 g/kg of S35-DMSO. Two animals each were sacrificed after 30 min, 1 hr, 2 hr and 24 hr respectively.
In rats, after 30 min, 63% (average) of the dose remained at the site of application; after 1 hr, 19% (average) of the dose remained; and, after 2 hr, 14% (average) was left. After 24 hr, the radioactivity at the site of application was the same as that of the surrounding skin.
Six rabbits were similarly treated. In 2 animals, sacrificed after 30 min, 85% (average) of the dose remained at the site of application. After 4 hr, 11% (average) remained, and, after 24 hr, the radioactivity was essentially equal to that of the surrounding skin.

Disposition of S35-DMSO in rat tissues:
S35-DMSO was administered to rats orally and dermally, the animals were killed at various times and the tissues were assayed for total radioactivity (tables 1 and 2). There were

appreciable concentrations of radioactivity in all tissues 0.5 hr after an oral dose. Plasma, kidney, spleen, lung, heart and testes appeared to have somewhat higher levels than liver, fat, small intestine, brain, skeletal muscle and red cells.
Concentrations in the testes, brain skeletal muscle and heart increased after 0.5 hr, but remained virtually constant in other tissues. Levels had declined to minimal values in all tissues after 24 hr.
Concentrations of DMSO and DMSO2 in selected tissues were estimated by extraction and thin layer chromatography. The ratio of DMSO2 to DMSO in rats 4 hr after oral administration of S35-DMSO was found to be virtually constant in liver, testes, kidney, spleen, small intestine, heart and plasma, averaging about 6.5% (range of 4.1-10.6% for tissues of 2 rats). The recovery of radioactivity from these tissues was, in all cases, virtually identical with that obtained when S35-DMSO and S35-DMSO2 were added to tissues in amounts equivalent to those present in rats given S35-DMSO. Thus, the major part, at least, of radioactivity present in tissues seems to be represented by DMSO.
After dermal administration, tissue concentrations of radioactivity were also appreciable after 0.5 hr, but were somewhat lower than after an oral dose. In this case, levels in the plasma, spleen, liver and lungs were higher than the other tissues. Concentrations in the liver, testes, kidney, spleen, brain, lungs, skeletal muscle, heart, plasma and red cells increased after 4 hr to values comparable to those after an oral dose. Levels in the fat and small intestine remained virtually constant. All tissue concentrations had declined to minimal values after 24 hr.

Disposition of S35-DMSO in rabbit tissues:
S35-DMSO was administered dermally to rabbits. The animals were killed at various times and the tissues were assayed for total radioactivity (table 3). Concentrations of radioactivity were appreciable after 0.5 hr in all tissues except the lens. The levels were lower than those seen in the rat, except for the testes which were equivalent.
Concentrations in all tissues increased sharply after 4 hr to values that were 3 to 60 times higher than at 0.5 hr. Levels in the lungs, heart, plasma, bile; aqueous humor, vitreous humor and cornea were higher than those in other tissues.
Concentrations in the fat tended to remain lower than in other tissues. After 24 hr, the level had declined, but remained somewhat higher than corresponding levels in the rat.
Concentrations of DMSO and DMSO2, in selected tissues were also estimated by extraction and thin layer chromatography.
The ratio of DMSO2 to DMSO in rabbits 4 hr after dermal administration of S35-DMSO appeared to be slightly higher than in rats, averaging 11.6% (range of 0-18%) for testes, brain plasma, bile, aqueous humor, lens, vitreous humor and the area of skin at the site of application. The ratio in liver and kidney was slightly higher, averaging 21% (range of 14-26%) in 2 animals.

Excretion of radioactivity following S35-DMSO administration:
Rats received S35-DMSO dermally, orally and intraperitoneally. Rabbits and guinea pigs were given S35-DMSO dermally and intraperitoneally respectively. Urine and feces

were collected for 24 hr and assayed for total radioactivity (table 4). Approximately 67 % of the dose was excreted in rat urine within 24 hr and 4 to 10% in the feces. Rabbits excreted 30% of the dose in the urine in 24 hr. Guinea pigs excreted an average of 52% of the dose in the urine in 24 hr and 4% of the dose in the feces. An additional 16% of the dose was excreted by guinea pigs in 24 to 48 hr.
Radioactivity in respired air was measured from 2 rats given 0.55 g/kg of S35-DMSO (approximately 8 µC) dermally. An average of 6.0% of the dose was found in the respired air assayed over a 24-hr period following dosing. Less than 1% of the dose was found in the respired air of a rabbit monitored over a 3-hr period following an intraperitoneal dose of 0.55 g/kg (4 µC).

Identification of DMSO and DMSO2 in urine
The amount of DMSO2 in rat urine was estimated quantitatively. S35-DMSO (0.55 g/kg, 2.5 µC) was given to each of 3 rats intraperitoneally, and the 24-hr urine was collected and used for determination of DMSO2.
DMSO2 was found in an amount which represented an average of 12.8% of the administered DMSO. Total radioactivity in the urine represented an average of 75.8% of the dose.
Urine from rabbits and guinea-pigs given 0.55 g/kg of S35-DMSO dermally or intraperitoneally, respectively, was collected for 24 hr. DMSO and DMSO2 were identified in the urine.

Source : Atofina, Paris-la-Défense, France.
Atofina Paris La Défense Cedex

Attached document : Hucker figures 1 and 2.bmp
Hucker figure 3.bmp
Hucker figure 4.bm p

TABLE 1

Total radioactivity in rat tissues at various times after oral administration of S^{35}-DMSO

Tissue	Total Radioactivity							
	0.5 hr				4 hr		24 hr	
	1	2	3	4	5	6	7	8
Plasma	284	585	691	821	652	625	81	67
Liver	0.65	0.40	0.53	0.65	0.62	0.56	0.98	0.65
Testes	0.55	0.50	0.59	0.69	0.85	0.87	1.06	0.87
Fat	0.51	0.60	0.50	0.32	0.50	0.43	0.42	0.30
Kidney	0.58	0.76	0.70	0.75	0.67	0.69	1.18	0.80
Spleen	0.66	0.66	0.65	0.71	0.50	0.67	1.14	0.72
Small intestine	0.45	0.55	0.38	0.48	0.49	0.39	1.06	0.62
Brain	0.47	0.52	0.50	0.53	0.68	0.70	1.12	0.69
Lungs	0.71	0.72	0.81	0.75	0.67	0.70	1.02	0.69
Skeletal muscle	0.50	0.55	0.46	0.58	0.63	0.57	1.19	0.78
Heart	0.64	0.71	0.60	0.73	0.71	0.75	1.12	0.86
Red cells	0.52	0.49	0.56	0.62	0.46	0.54	0.89	0.65

Eight rats received 0.55 g/kg (approximately 7 µc) of S^{35}-DMSO orally. Four animals were killed after ½ hr, and 2 each after 4 and 24 hr. Tissues were assayed for total radioactivity. Results for plasma are expressed as microgram equivalents of DMSO per gram of tissue, and the remaining tissue concentrations are expressed as the ratio of the tissue level to the corresponding plasma concentration.

TABLE 2

Total radioactivity in rat tissues at various times after dermal administration of S^{35}-DMSO

Tissue	Total Radioactivity							
	0.5 hr		4 hr				24 hr	
	1	2	3	4	5	6	7	8
Plasma	320	302	393	565	417	445	65	70
Liver	0.62	0.78	0.62	0.60	0.71	0.65	0.62	0.56
Testes	0.34	0.43	0.86	0.86	0.89	0.94	0.88	0.86
Fat	0.59	0.40	0.14	0.32	0.57	0.36	0.64	0.53
Kidney	0.59	0.64	0.66	0.74	0.92	0.77	0.80	0.76
Spleen	0.76	0.66	0.71	0.76	0.77	0.77	0.66	0.65
Small intestine	0.60	0.50	0.48	0.49	0.45	0.42	0.38	0.42
Brain	0.53	0.54	0.72	0.73	0.71	0.76	0.74	0.69
Lungs	0.63	0.75	0.66	0.70	0.92	0.82	0.76	0.67
Skeletal muscle	0.53	0.36	0.39	0.74	0.80	0.77	0.72	0.56
Heart	0.66	0.66	0.68	0.66	0.87	0.89	0.69	0.72
Red cells	0.54	0.58	0.56	0.56	0.61	0.75	0.53	0.48

Eight rats received 0.55 g/kg (approximately 11 µc) of S^{35}-DMSO dermally. Two animals were killed after ½ hr, 4 animals after 4 hr and 2 animals after 24 hr. Tissues were assayed for total radioactivity. Results for plasma are expressed as microgram equivalents of DMSO per gram of tissue, and the remaining tissue concentrations are expressed as the ratio of the tissue level to the corresponding plasma concentration.

TABLE 3

Total radioactivity in rabbit tissues after dermal administration of S^{35}-DMSO

Tissue	Total Radioactivity					
	0.5 hr		4 hr		24 hr	
	1	2	3	4	5	6
Plasma	93	124	472	530	117	213
Liver	0.32	0.60	0.52	0.38	0.69	0.63
Testes	1.81	0.57	0.61	0.55	0.84	0.82
Fat	0.27	0.12	0.15	0.13	0.20	0.10
Kidney	0.27	0.56	0.69	0.46	0.89	0.82
Spleen	1.25	0.62	0.65	0.61	0.90	0.95
Small intestine	0.30	0.54	0.65	0.60	0.85	0.89
Brain	0.40	0.48	0.65	0.61	0.63	0.66
Lungs	0.66	0.75	0.73	0.58	0.72	0.72
Skeletal muscle	0.46	0.38	0.63	0.59	0.75	0.74
Heart	0.76	1.02	0.69	0.63	0.77	0.77
Red cells	0.22	0.57	0.55	0.59	0.61	0.66
Bile	0.57	0.98	1.77	0.88	1.40	0.84
Aqueous humor	0.47	0.56	0.92	0.91	1.06	1.14
Vitreous humor	0.29	0.43	0.96	0.80	0.88	0.98
Lens	0.09	0.05	0.22	0.20	0.53	0.54
Cornea	0.54	0.69	0.91	0.95	0.85	0.91
Skin	1.30	0.60	0.52	0.36	1.12	1.00

Six rabbits received 0.55 g/kg (approximately 7 μc) of S^{35}-DMSO dermally. Two animals were killed after ½ hr, 2 were killed after 4 hr and 2 were killed after 24 hr. Tissues were assayed for total radioactivity. Results for plasma are expressed as microgram equivalents of DMSO per gram of tissue, and the remaining tissue concentrations are expressed as the ratio of the tissue level to the corresponding plasma concentration.

TABLE 4

Excretion of total radioactivity after administration of S^{35}-DMSO by various routes to rats and rabbits

Species	Route of Administration	Total Radioactivity	
		Urine	Feces
		%	%
Rat	Oral	67 (50–77)	10 (1–14)
Rat	Dermal	66 (64–67)	4 (2–7)
Rat	Intraperitoneal	68 (60–73)	4 (1–9)
Rabbit	Dermal	30 (20–40)	
Guinea pig	Intraperitoneal	52 (49–55)	4 (2–5)

Three rats received 0.55 g/kg (approximately 0.9 μc) of S^{35}-DMSO orally, 3 received the same dose intraperitoneally and 3 received 0.55 g/kg (approximately 5 μc) dermally. Two rabbits received 0.55 g/kg (approximately 7 μc) of S^{35}-DMSO dermally. Two guinea pigs were given 0.55 g/kg (approximately 5 μc) of S^{35}-DMSO intraperitoneally. Urine and feces were collected for 24 hr and assayed for total radioactivity. *Results are expressed as percentage of the radioactivity administered.* Average values are given with the range shown in brackets.

Conclusion : DMSO is rapidly and well absorbed when administered orally or dermally to rats or rabbits. Plasma levels of radioactivity following a dermal dose of S35-labeled DMSO to rats reach a maximum value after 2 hr, comparable to the level reached approximately 1 hr after either oral or intraperitoneal administration. Approximately 67 % of the administered radioactivity is excreted in the urine of rats within 24 hr, somewhat less than this in the

rabbit and guinea pig. The rate of dermal absorption is apparently somewhat faster in the rat than in the rabbit. Radioactivity is rapidly and widely distributed in the tissues of rats and rabbits following administration of labelled DMSO. The levels of radioactivity declined to relatively low values after 24 hr in the rat but remained somewhat higher in the rabbit, suggesting possible accumulation in the latter species. Of particular interest is the finding in the rabbit of relatively high concentrations of radioactive material in the various ocular tissues.
The tissue levels of DMSO are roughly equivalent in blood, testis, spleen, liver, kidney and brain. About 10 to 15% of administered DMSO is metabolized to DMSO2 by the rat. Both the DMSO2 and unchanged DMSO are excreted chiefly in the urine. Quantitative gas chromatographic analysis (unpublished data, Hucker et al.) of the urine of rats given S35-labeled DMSO indicates that unchanged DMSO and DMSO2 account for all theradioactivity present in the urine. DMSO was also shown converted to the DMSO2 by rabbits and guinea pigs. Excretion of DMS0 is less rapid in the rabbit than in the rat, suggesting that accumulation of both DMSO and DMSO2 may occur in the rabbit. Quantitative gas chromatographic studies (unpublished data, Hucker et al.) show that the urinary excretion pattern of DMSO and DMSO2 in rabbits differs from that in rats. In rabbits given DMSO dermally (0.55 g/kg), excretion of DMSO was complete within 24 hr and represented 30% of the dose. Excretion of DMSO2, however, continued over a period of 5 days and amounted to 23% of the dose. Excretion of DMS0 and DMSO2 in the guinea pig was net as extensively studied, but preliminary results (unpublished) suggest that it resembles the rabbit in this respect. Ratios of DMSO2 to DMSO excreted in 24 hr ranged from 0.2 to 0.5.

Reliability : (2) valid with restrictions
12.08.2003

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 28300 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male/female
Number of animals	:	30
Vehicle	:	other: none
Doses	:	10, 20, and 40 g/kg
Method	:	other
Year	:	1965
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Single oral doses of undiluted DMSO were administered by gavage to groups of 5 male and 5 female Carworth CFN rats. Dose levels were 10, 20, and 40 g/kg. Animals were fasted for 16-18 hr prior to DMSO administration. Animals were observed for 14 days following administration of DMSO. Median lethal dose (LD50), 95% confidence limit, and probit slopes were determined.

Result : With one exception, all deaths occurred within the first 24 hours. Lethal doses caused ataxia, myasthenia, decreased motor activity, and bradypnea shortly after administration. Non-lethal doses of DMSO produced decreased motor activity, although polydipsia and polyuria were noted in rats following doses of 20 g/kg. The LD50 was determined to be 28.3 g/kg.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
22.07.2003 (154)

Type : LD50
Value : = 17100 - 26900 mg/kg bw
Species : mouse
Strain :
Sex : male/female
Number of animals : 30
Vehicle : other: none
Doses : 10, 20, and 40 g/kg
Method : other
Year : 1965
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Single oral doses of undiluted DMSO was administered by gavage to groups of 5 male and 5 female albino mice. Dose levels were 10, 20, and 40 g/kg. Animals were fasted for 16-18 hr prior to DMSO administration. Animals were observed for 14 days following administration of DMSO.
Median lethal dose (LD50), 95% confidence limit, probit slopes, and maximum tolerated dose (LD0.1) were determined.
Result : With one exception, all deaths occurred within the first 24 hours. Death was preceded by ataxia, myasthenia, decreased motor activity, and bradypnea. Non-lethal doses of DMSO produced decreased motor activity.
The LD50 was determined to be 21.4 g/kg; the 95% confidence limits were 17.1 - 26.9 g/kg. The LD0.1 was calculated to be 9.42 g/kg.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
24.12.2002 (154)

Type : LD50
Value : > 22000 mg/kg bw
Species : rat
Strain :
Sex : male/female
Number of animals :
Vehicle : no data
Doses :
Method : other: no data
Year : 1963
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : 20 ml/kg killed one of four animals in a group of male and also in a group of female rats. Below this dose there were no deaths.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
Documentation insufficient for assessment
24.12.2002 (23)

Type : LD50
Value : = 13400 - 15700 mg/kg bw
Species : rat
Strain :
Sex : no data
Number of animals : 72
Vehicle : other
Doses :
Method : other: no data
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : LD50 was calculated 14.5 g/kg. Hyperemia and inflammation of the eyes were noted in animals receiving 13 g/kg or more
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
Documentation insufficient for assessment
24.12.2002 (59)

Type : LD50
Value : = 19250 - 22000 mg/kg bw
Species : mouse
Strain :
Sex : no data
Number of animals : 8
Vehicle : other: undiluted
Doses :
Method : other: no data
Year : 1963
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : This small experiment indicated that the acute oral toxicity of DMSO to mice was similar to that of rats. 1/4 mice died at a dose of 17.5 ml/kg, and 2/4 died at 20.0 ml/kg.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
Documentation insufficient for assessment
24.12.2002 (23)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC0
Value : > 1.6 mg/l
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals : 8
Vehicle : other: none
Doses : 1.6 mg/l
Exposure time : 4 hour(s)

Method : other: no data
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Three groups of 8 male Sprague-Dawley rats were exposed to an aerosol of 1600 mg DMSO per cubic meter of air for 4 hr. Control rats were exposed to a normal chamber environment.

One groups were sacrificed immediately after exposure, another 24 hr after exposure, and the third group was observed for 2 weeks after exposure before sacrifice.

All animals were examined for signs of toxicity before, during, and after exposure. Blood was obtained prior to and after exposure. Animals were sacrificed and organs examined; and blood and tissues obtained for biochemical analyses and histologic examination.

Result : There was no mortality and none of the animals displayed outward signs of toxicity during and after exposure to DMSO. After exposure, the hair was damp and slightly yellow, and the animals had a characteristic garlic-like odor.

Organs appeared normal at necropsy. Histopathologic examination revealed areas of hemorrhage in lung sections of control and DMSO treated animals. Focal and diffuse collections of clear pneumocytes were noted within lung alveoli in DMSO treated rats; similar edematous changes were not seen in control animals.

Biochemical and hematological analyses did not reveal any deviations that could be ascribed to DMSO exposure.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
22.07.2003 (59)

Type : LC0
Value : > 2.9 mg/l
Species : rat
Strain : Sprague-Dawley
Sex : male
Number of animals : 8
Vehicle : other: no data
Doses : 2.9 mg/l
Exposure time : 24 hour(s)
Method : other
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A group of 8 male Sprague-Dawley rats was exposed to 2900 mg/m3 for 24 hours and sacrificed immediately after exposure. Control rats were exposed to a normal chamber environment.

All animals were examined for signs of toxicity before, during, and after exposure. Blood was obtained prior to and after exposure. Animals were sacrificed and organs examined; and blood and tissues obtained for biochemical analyses and histologic examination.

Result : There was no mortality and none of the animals displayed

outward signs of toxicity during and after exposure to DMSO. After exposure, the hair was damp and slightly yellow, and the animals had a characteristic garlic-like odor.

Organs appeared normal at necropsy. Histopathologic examination revealed areas of hemorrhage in lung sections of control and DMSO treated animals. Areas of pulmonary edema were seen in some treated animals but not in control animals.

Biochemical and hematological analyses did not reveal any deviations that could be ascribed to DMSO exposure, with the possible exception of elevated serum urea nitrogen in rats exposed to 2900 mg/m3.

Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

12.08.2003 (59)

Type : LC0
Value : > 2 mg/l
Species : rat
Strain :
Sex : male
Number of animals : 8
Vehicle : other: none
Doses : 2.0 mg/l
Exposure time : 40 hour(s)
Method : other
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A group of 8 male Sprague-Dawley rats was exposed to 2000 mg/m3 for 40 hours and sacrificed immediately after exposure.
Control rats were exposed to a normal chamber environment.

All animals were examined for signs of toxicity before, during, and after exposure. Blood was obtained prior to and after exposure. Animals were sacrificed and organs examined; and blood and tissues obtained for biochemical analyses and histologic examination.

Result : There was no mortality and none of the animals displayed outward signs of toxicity during and after exposure to DMSO. After exposure, the hair was damp and slightly yellow, and the animals had a characteristic garlic-like odor.

Organs appeared normal at necropsy. Histopathologic examination revealed areas of hemorrhage in lung sections of control and DMSO treated animals. Focal and diffuse collections of clear pneumocytes were noted within lung alveoli in DMSO treated rats; similar changes were seen in control animals, but less frequently. Areas of pulmonary edema were seen in some exposed animals, similar edematous changes were not noted in control animals.

Biochemical and hematological analyses did not reveal any deviations that could be ascribed to DMSO exposure.

Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
22.07.2003 (59)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Value : ca. 40000 mg/kg bw
Species : rat
Strain :
Sex : male/female
Number of animals :
Vehicle : water
Doses :
Method : other:
Year : 1968
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 4 to 14 unshaven rats (108-182 g) were immersed in a DMSO solution (40, 60, 80 or 100%) until the fur and the skin were thoroughly wetted. The animals were then withdrawn from the solution and allow most of the excess solution to run off. From th e weights before and after dipping, it was possible to calculate the amount of DMSO.
Result : There was no immediate response, but within 24 hours 13/14 rats dipped into 100% DMSO were dead. A complete microscopic examination of tissues revealed no changes.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
Significant methodological deficiences
22.07.2003 (133)

Type : LD50
Value : ca. 50000 mg/kg bw
Species : mouse
Strain :
Sex : male/female
Number of animals :
Vehicle : water
Doses :
Method : other
Year : 1968
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 4 to 6 unshaven mice (13-28 g) were immersed in a DMSO solution (40, 60, 80 or 100%) until the fur and the skin were thoroughly wetted. The animals were then withdrawn from the solution and allow most of the excess solution to run off. From the weights before and after dipping, it was possible to calculate the amount of DMSO.
Result : There was no immediate response, but within 24 hours all mice dipped into 100% DMSO were dead.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
Significant methodological deficiences
24.12.2002 (133)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	= 5360 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	male/female
Number of animals	:	30
Vehicle	:	other: none
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	1 minute(s)
Method	:	other
Year	:	1965
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Single i.v. injections of undiluted DMSO were administered to groups of 5 male and 5 female Carworth CFN rats. Dose levels were 2.5, 5.0, and 10 g/kg. Each dose was administered over a 1-minute interval. Animals were observed for 14 days following DMSO administration. Median lethal dose (LD50), 95% confidence limit, probit slopes and maximum tolerated dose (LD0.1) were determined.
Result	:	With one exception, deaths occurred within the first 24 hours. Death was preceded by tremors, myasthenia, dyspnea, and occassionally, convulsions. Non-lethal doses of DMSO produced decreased motor activity and myasthenia. The LD50 was determined to be 5.36 g/kg; the LD0.1 was calculated to be 2.35 g/kg.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

24.12.2002 (154)

Type	:	LD50
Value	:	= 5750 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	male/female
Number of animals	:	30
Vehicle	:	other: none
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	1 minute(s)
Method	:	other
Year	:	1965
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Single i.v. injections of undiluted DMSO were administered to groups of 5 male and 5 female albino mice. Dose levels were 2.5, 5.0, and 10 g/kg. Each dose was administered over a 1-minute interval. Animals were observed for 14 days following DMSO administration. Median lethal dose (LD50), 95% confidence limit, probit slopes and maximum tolerated dose (LD0.1) were determined.
Result	:	With one exception, deaths occurred within the first 24 hours. Death was preceded by tremors, myasthenia, dyspnea, and occassionally, convulsions. Non-lethal doses of DMSO produced decreased motor activity and myasthenia.

		The LD50 was determined to be 5.75 g/kg; the LD0.1 was calculated to be 2.74 g/kg.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

24.12.2002 (154)

Type	:	LD50
Value	:	= 3100 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	no data
Number of animals	:	41
Vehicle	:	other: Hank's balanced salt solution
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	
Method	:	other : no data
Year	:	1969
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Range of values = 2700 - 3500 mg/kg.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

24.12.2002 (59)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	not irritating
Method	:	Draize Test
Year	:	1969
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Essentially no effect was observed when DMSO was applied topically other than a slight erythema which faded quickly after removal of the taped patch.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

26.02.2003 (60)

Species	:	guinea pig
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	
PDII	:	1.2
Result	:	slightly irritating
Classification	:	not irritating

Method : OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year : 1995
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (138)

Species : mouse
Concentration : undiluted
Exposure : Open
Exposure time :
Number of animals : 5
Vehicle :
PDII :
Result : not irritating
Classification : not irritating
Method : other
Year : 1963
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Undiluted DMSO was painted on to the dorsal scapula region of 5 male AH mice twice a week for 30 weeks.
Result : At the end of the exposure period, no discernable effect on the skin was observed.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
22.07.2003 (24)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure time : 24 hour(s)
Comment :
Number of animals :
Vehicle :
Result : slightly irritating
Classification : not irritating
Method : Draize Test
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Slight conjunctivitis in the eyes of rabbits were noted at the 24 hr observation period in the animals undergoing ocular tests. This had disappeared by 48 hrs.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (59)

Species : rabbit
Concentration : undiluted
Dose : .1 ml

Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	6
Vehicle	:	
Result	:	slightly irritating
Classification	:	not irritating
Method	:	Directive 84/449/EEC, B.5 "Acute toxicity (eye irritation)"
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	DMSO produced slight erythema of the conjunctiva over the first three days of the study, and a low level of key scoring was also recorded for chemosis, iritis and corneal opacity. The degree of eye injury described by these key scores would not result in DMSO being labelled as an eye irritant according EEC classification.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

24.12.2002 (80)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	4
Vehicle	:	
Result	:	slightly irritating
Classification	:	not irritating
Method	:	Draize Test
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Pure DMSO is only slightly irritant and no irritation was observed after 1 day.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

24.12.2002 (36)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	3
Vehicle	:	
Result	:	slightly irritating
Classification	:	not irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1992
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	DMSO induced a very slight conjunctival irritation which cleared in 3 days.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

24.12.2002 (97)

5.3 SENSITIZATION

Type : Guinea pig maximization test
Species : guinea pig
Concentration : 1st: Induction undiluted intracutaneous
2nd: Induction undiluted open epicutaneous
3rd: Challenge undiluted open epicutaneous
Number of animals : 10
Vehicle : other: none
Result : not sensitizing
Classification : not sensitizing
Method : OECD Guide-line 406 "Skin Sensitization"
Year : 1994
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (111)

Type : Buehler Test
Species : guinea pig
Concentration : 1st: Induction 10 % intracutaneous
2nd: Challenge 10 % intracutaneous
3rd:
Number of animals : 7
Vehicle : water
Result : not sensitizing
Classification : not sensitizing
Method : other: no data
Year : 1963
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (24)

Type : Mouse ear swelling test
Species : mouse
Concentration : 1st: Induction undiluted open epicutaneous
2nd: Challenge undiluted open epicutaneous
3rd:
Number of animals :
Vehicle : other: none
Result : not sensitizing
Classification : not sensitizing
Method : other
Year : 1986
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (64)

Type	:	Mouse local lymphnode assay
Species	:	mouse
Concentration	:	1st: Induction 100 % active substance open epicutaneous 2nd: 3rd:
Number of animals	:	3
Vehicle	:	other: none
Result	:	
Classification	:	
Method	:	other
Year	:	1993
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Exposure of groups of 3 mice to pure DMSO (concentration 20 and 50 % being ineffective) induced a small increase (approximately 2-fold) in LNC proliferation compared with the water-solution treated group.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(2) valid with restrictions

24.12.2002 (78)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	monkey
Sex	:	male/female
Strain	:	other: Macaca mulatta (rhesus)
Route of admin.	:	gavage
Exposure period	:	18 months
Frequency of treatm.	:	daily
Post exposure period	:	None
Doses	:	1 - 3 - 9 ml of 90% DMSO solution/kg (990 - 2970 - 8910 mg/kg)
Control group	:	other: water, 9 ml/kg
NOAEL	:	= 3300 mg/kg bw
LOAEL	:	= 9900 mg/kg bw
Method	:	other: no data
Year	:	1970
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Pharmaceutical-grade DMSO was administered as a 90% solution to 4 groups of rhesus monkeys by gastric intubation, 7 days a week for up to 87 weeks. One half the dose was administered in the morning, the remainder was given in late afternoon. Groups of 2 animals of each sex were treated with 1 or 3 ml/kg. Three animals of each sex received 9 ml/kg. Dosages administered were equivalent to 990, 2970, and 8910 mg/kg/day. Examinations included water consumption, clinical chemistry, hematology, urinalysis, EKG, reflexes, and body weight. All animals were subjected to a detailed necropsy. Organs were weighed and tissues prepared for histological examination. Doses of 0, 1, 3, and 9 ml/kg of a 90 % (v/v) aqueous solution of pharmaceutical grade DMSO (these dosages were equivalent to 0, 0.99, 2.97, and 8.91 g/kg per day,

respectively) were administered to 4 groups of rhesus monkeys by gastric intubation 7 days per week. One half of the indicated dose was given in the morning and the other half in the late afternoon. Control animais in each group were given water, 9.0 ml/kg body weight.
There were 2 females and 1 male in the oral control group, 2 animals of each sex in the groups treated with 1 and 3 ml/kg, and 3 animals of each sex in the groups receiving 9 ml/kg per day of DMSO. One monkey was kept in separate rooms to preclude the possibility of inhaling DMSO or its metabolites from treated animals. Physical signs, behavior, and survival time were recorded daily. The monkeys were given a nutritionally adequate laboratory ration (Purina Monkey Chow) supplemented with fresh fruit daily and water ad libitum.
Examinations included water consumption, electrocardiogram, neurologic (reflexes), heart rate, body weight, blood pressure, body temperature, respiratory rate, and ophthalmologic. Complete blood counts, serum glutamic-pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP), blood urea nitrogen (BUN), blood glucose, 45-minute sulfobromophthalein (BSP) retention, and endogenous creatinine clearance were measured in all animals. Urinalysis consisted of specific gravity, pH, albumin, glucose, occult blood, ketone bodies, and microscopic examination of the sediment. All of these determinations were performed in accordance with standard procedures.
Because of the need to schedule the broad spectrum of clinical determinations in each animal, starting dates for dosing were staggered over a 6-week period. Surviving monkeys were treated for 74-87 weeks.
All animals that died or were sacrificed were submitted for a detailed necropsy. The following organs were weighed: liver, kidneys, heart, brain, gonads, prostate or uterus, adrenals, thyroid, pituitary, and lungs.
Histomorphologic examinations were performed on the following hematoxylineosin-stained sections of formalin-fixed tissues: liver, spleen, stomach (including fundus and pyloric regions), small intestine (including duodénum, jejunum, and ileum), large intestine (including colon and cecum), pancreas, kidneys, bladder, adrenals, gonads, thyroid, pituitary, thymus, salivary glands, lymph nodes (including cervical and mesenteric), heart, lungs, femoral bone marrow, skin, skeletal muscle, spinal cord, brain, gallbladder, epididymis, seminal vesicles, prostate, uterus, aorta, larynx, trachea, peripheral nerve, diaphragm, and lacrimal glands. The eyes were fixed in formalin or Zenker's fixative. Bone marrow smears were stained with Wright's stain.

Result : The highest oral dose, 9 ml/kg per day, was not well tolerated by 6 monkeys in this group; 1 died accidently and 5 succumbed as a result of treatment with DMSO. The 1 and 3 ml/kg doses were well tolerated, and the animais were sacrificed with the control monkeys at the end of the study.

The principal physical signs seen in the animals given DMSO orally included ptyalism and emesis. These signs occurred sporadically and did not appear to be related to the dose except in the group receiving 9 ml/kg. Also, they were observed in the control group, although less frequently. Anorexia occurred at high oral doses but was not evident at

the 2 lower dose levels. Some monkeys in all treated gr oups had erythema of the skin.

Monkeys given 1 and 3 ml/kg orally, showed slightly less gain in mean body weight compared to the respective control animals during the study. However, no biologic significance is attached to these differences because of the limited number of animals per group and the wide range of initial weights.
Marked losses in body weight occurred in animals given 9 ml/kg DMSO orally. Most severe losses were during the first 6 weeks of study when emesis and anorexia occurred. One monkey lost 1 kg of weight during week 1 and 1.6 kg by week 12. The remaining monkeys generally showed slight gains in body weight after week 6, but all weighed less at death than when the study began.

No DMSO-related changes were found in the treated monkeys during physical examinations. These tests included mean systolic blood pressure, heart rate, respiratory rate, body temperature, 48-hour water consumption, neurological reflexes, and electrocardiograms, performed during weeks 1, 4, 7, 12, 24, 37, 51, and 73 of study.
No evidence of refractoriness to Tropicamide mydriasis was seen in any of these monkeys. The typical DMSO lenticular changes described in other species were not visible in any monkey during the course of the experiment.

The mean hematologic results at approximately 6-month intervals are presented for the control and 3 ml/kg groups in Table 1. Table 2 shows the biochemical data for the same groups. No significant différences were found between the DMSO-treated and control monkeys in any of the hematologic or biochemical parameters evaluated. Animals given 1 ml/kg orally responded in a similar manner. Although values for the animals receiving 9 ml/kg orally are not shown, the data agree with those reported for the control and other test groups. At n o time were any abnormal hematologic or biochemical results seen in the animais given the high oral dosage of DMSO.

Further, no significant différences were seen in erythrocyte sedimentation rate (ESR), BSP retention, creatinine clearance, urinalysis, and absolute or relative organ weights between the treated and control animals.

No significant lesions attributable to DMSO were found upon gross examination at necropsy.

No histologic changes were visible in the lenses of treated animals.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Attached document : Vogin Table 1.bmp
Vogin Table 2.bmp

TABLE 1

MEAN HEMATOLOGIC FINDINGS IN MONKEYS RECEIVING DMSO (90% v/v)

DMSO (ml/kg)	Route	Week of study	Total WBC (×10³/mm³)	Differential (%) P	L	Other	Hb (g/100 ml)	Hct (%)	Prothrombin time (sec)	Platelets (×10³/mm³)
0	Dermal	0	9.4	42	56	2	13.9	42	15.5	150
		26	7.2	23	75	2	12.3	40	12.2	110
		51	16.2	31	69	0	11.9	39	12.5	130
		73–78	7.0	48	52	0	11.9	40	20.7	130
9	Dermal	0	12.1	43	57	0	13.5	44	14.5	135
		26	6.8	34	62	4	14.3	41	12.7	145
		51	6.6	29	69	2	12.4	39	12.3	155
		73–78	6.8	40	59	1	12.8	41	14.8	150
0	Oral	0	9.7	36	63	1	14.2	45	14.3	120
		26	7.1	36	61	3	13.6	46	12.6	200
		52	6.7	43	50	7	11.9	40	13.6	170
		78	7.5	42	57	1	13.1	43	14.9	150
3	Oral	0	11.2	47	53	0	14.9	42	14.2	120
		26	5.3	27	71	2	12.3	40	13.0	150
		52	8.1	28	65	7	12.5	40	13.0	150
		78	7.2	33	66	1	13.5	42	14.9	120

TABLE 2

MEAN BIOCHEMICAL FINDINGS IN MONKEYS RECEIVING DMSO (90% v/v)

DMSO (ml/kg)	Route	Week of study	BUN (mg/100 ml)	Glucose (mg/100 ml)	SGPT (units)	SAP (units)
0	Dermal	0	16	73	17	11.9
		26	39	87	20	27.1
		51	25	85	39	10.8
		73–78	24	68	25	6.1
9	Dermal	0	14	73	17	12.7
		26	32	83	21	19.1
		51	27	70	35	14.2
		73–78	25	72	18	6.4
0	Oral	0	16	67	21	12.0
		26	23	105	19	18.7
		52	14	72	37	12.5
		78	18	74	19	8.8
3	Oral	0	17	104	18	16.3
		26	17	100	29	20.5
		52	20	102	27	10.8
		78	22	90	17	5.2

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

12.08.2003

Type	:	
Species	:	monkey
Sex	:	male/female
Strain	:	other: Macaca mulatta (rhesus)
Route of admin.	:	dermal
Exposure period	:	18 months
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	1 - 3 - 9 ml of 90% DMSO solution/kg (990 - 2970 - 8910 mg/kg)
Control group	:	other: water, 9 ml/kg
NOAEL	:	= 8910 mg/kg
Method	:	other
Year	:	1970
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method :

Doses (0, 1, 3, and 9 ml/kg) of a 90 % (v/v) aqueous solution of pharmaceutical grade DMSO were administered dermally to 4 groups of rhesus monkeys 7 days per week. Topical administration was by direct application to the entire abdominal skin. Animals were restrained in a supine position for 1 hour after drug administration to prevent ingestion of the applied solution. Control animals in each group were given water, 9.0 ml/kg body weight. Dosages administered were equivalent to 990, 2970, and 8910 mg/kg/day.

There were 2 males and 1 female in the control group, 2 animals of each sex in the groups treated with 1 and 3 ml/kg, and 3 animals of each sex in the groups receiving 9 ml/kg per day of DMSO. One monkey was kept in separate rooms to preclude the possibility of inhaling DMSO or its metabolites from treated animals.

Physical signs, behavior, and survival time were recorded daily. The monkeys were given a nutritionally adequate laboratory ration (Purina Monkey Chow) supplemented with fresh fruit daily and water ad libitum.
Examinations included water consumption, electrocardiogram, neurologic (reflexes), heart rate, body weight, blood pressure, body temperature, respiratory rate, and ophthalmologic. Complete blood counts, serum glutamic-pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP), blood urea nitrogen (BUN), blood glucose, 45-minute sulfobromophthalein (BSP) retention, and endogenous creatinine clearance were measured in all animals. Urinalysis consisted of specific gravity, pH, albumin, glucose, occult blood, ketone bodies, and microscopic examination of the sediment. All of these determinations were performed in accordance with standard procedures.

Because of the need to schedule the broad spectrum of clinical determinations in each animal, starting dates for dosing were staggered over a 6-week period. Surviving monkeys were treated for 74-87 weeks.

All animals that died or were sacrificed were submitted to a detailed necropsy. The following organs were weighed: liver, kidneys, heart, brain, gonads, prostate or uterus, adrenals,

thyroid, pituitary, and lungs.
Histomorphologic examinations were performed on the following hematoxylineosin-stained sections of formalin-fixed tissues: liver, spleen, stomach (including fundus and pyloric regions), small intestine (including duodénum, jejunum, and ileum), large intestine (including colon and cecum), pancreas, kidneys, bladder, adrenals, gonads, thyroid, pituitary, thymus, salivary glands, lymph nodes (including cervical and mesenteric), heart, lungs, femoral bone marrow, skin, skeletal muscle, spinal cord, brain, gallbladder, epididymis, seminal vesicles, prostate, uterus, aorta, larynx, trachea, peripheral nerve, diaphragm, and lacrimal glands. The eyes were fixed in formalin or Zenker's fixative. Bone marrow smears were stained with Wright's stain.

Result : Several accidental deaths (self-strangulation) occurred as a result of vigorous attempts to escape by monkeys restrained in a supine position. Two monkeys that died early in the study were replaced. Two in the treated and 2 in the control groups that died or were sacrificed later were not replaced. In no instance was death attributed to the dermal treatment of these animals with DMSO.

All animals treated topically with DMSO exhibited scaling and flaking of the skin in the area of drug application during the initial phases of the study. There were no apparent differences among the various treatment groups. Although several animals had erythema of the skin it did not appear to be related to the dose, and erythema did not occur at regular internals in any animal. No other adverse behavioral or physical signs were seen that could be attributed to topical application of DMSO.

Monkeys given 1-9 ml/kg DMSO topically showed slightly less gain in mean body weight compared to the control animals during the study. However, no biologic significance is attached to these differences because of the limited number of animals per group and the wide range of initial weights.

No DMSO-related changes were found in the treated monkeys during physical examinations. These tests included mean systolic blood pressure, heart rate, respiratory rate, body temperature, 48-hour water consumption, neurological reflexes, and electrocardiograms, performed during weeks 1, 4, 7, 12, 24, 37, 51, and 73 of study.
No evidence of refractoriness to Tropicamide mydriasis was seen in any of these monkeys. The typical DMSO lenticular changes described in other species were not visible in any monkey during the course of the experiment. The only ocular abnormality observed was in one animal which had been given 1 ml of DMSO/kg per day dermally for 82 weeks. In the final ocular examination, this animal had a unilateral complete retinal detachment and syneresis of the vitreous humor. There were no biomicroscopically visible changes in the vitreous humor of the remaining animals.

The mean hematologic results at approximately 6-month intervals are presented for the topically treated control and 9 ml/kg groups in Table 1. Table 2 shows the biochemical data for the same groups. No significant differences were found between the DMSO-treated and control monkeys in any of the hematologic or biochemical parameters evaluated. Animals

given 1 or 3 ml/kg responded in a similar manner.

Further, no significant differences were seen in erythrocyte sedimentation rate (ESR), BSP retention, creatinine clearance, urinalysis, and absolute or relative organ weights between the treated and control animals.

No significant lesions attributable to DMSO were found upon gross examination at necropsy. Microscopic examination of the tissues showed tuberculosis in a control monkey in the dermally dosed group. This animal was sacrificed in week 41 because of a positive tuberculin reaction. Epidermal thickening and focal chronic hyperkeratosis were seen in skin sections of the abdomen from monkeys which had DMSO or water applied. This is often seen in animais treated dermally with aqueous solutions, and it is a result of constant application of fluid to the epidermis.
No histologie changes were visible in the lenses of treated animals with the exception of the monkey with retinal detachment. In this animal, there appeared to be several swollen lenticular fibers in the equatorial portion of the lens in the affected eyes. The retina was undergoing cystic changes and the outer limbs of the neuroepithelial cells were sticky. There was no indication of inflammatory activity within the eye although there was an accumulation of inflammatory cells in the periphery of the optic nerve near the globe.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Attached document : Vogin Table 1.bmp
Vogin Table 2.bmp

TABLE 1

MEAN HEMATOLOGIC FINDINGS IN MONKEYS RECEIVING DMSO (90% v/v)

DMSO (ml/kg)	Route	Week of study	Total WBC ($\times 30^3$/mm^3)	Differential (%) P	L	Other	Hb (g/100 ml)	Hct (%)	Prothrombin time (sec)	Platelets ($\times 30^3$/mm^3)
0	Dermal	0	9.4	42	56	2	13.9	42	15.5	150
		26	7.2	23	75	2	12.3	40	12.2	110
		51	16.2	31	69	0	11.9	39	12.5	130
		73–78	7.0	48	52	0	11.9	40	20.7	130
9	Dermal	0	12.1	43	57	0	13.5	44	14.5	135
		26	6.8	34	62	4	14.3	41	12.7	145
		51	6.6	29	69	2	12.4	39	12.3	155
		73–78	6.8	40	59	1	12.8	41	14.8	150
0	Oral	0	9.7	36	63	1	14.2	45	14.3	120
		26	7.1	36	61	3	13.6	46	12.6	200
		52	6.7	43	50	7	11.9	40	13.6	170
		78	7.5	42	57	1	13.1	43	14.9	150
3	Oral	0	11.2	47	53	0	14.9	42	14.2	120
		26	5.3	27	71	2	12.3	40	13.0	150
		52	8.1	28	65	7	12.5	40	13.0	150
		78	7.2	33	66	1	13.5	42	14.9	120

TABLE 2

MEAN BIOCHEMICAL FINDINGS IN MONKEYS RECEIVING DMSO (90% v/v)

MSO l/kg)	Route	Week of study	BUN (mg/100 ml)	Glucose (mg/100 ml)	SGPT (units)	SAP (units)
0	Dermal	0	16	73	17	11.9
		26	39	87	20	27.1
		51	25	85	39	10.8
		73–78	24	68	25	6.1
9	Dermal	0	14	73	17	12.7
		26	32	83	21	19.1
		51	27	70	35	14.2
		73–78	25	72	18	6.4
0	Oral	0	16	67	21	12.0
		26	23	105	19	18.7
		52	14	72	37	12.5
		78	18	74	19	8.8
3	Oral	0	17	104	18	16.3
		26	17	100	29	20.5
		52	20	102	27	10.8
		78	22	90	17	5.2

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
12.08.2003

Type :
Species : monkey
Sex : male
Strain : other: Macaca mulatta (rhesus)
Route of admin. : i.v.
Exposure period : 9 days consecutive
Frequency of treatm. : 1 x per day
Post exposure period : 120 days
Doses : 3 and 2 g/kg
Control group : yes, concurrent vehicle
Method : other: no data
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Daily i.v. doses of 3 or 2 g/kg DMSO in a 40% solution were given respectively to 4 or 1 male rhesus monkeys for 9 consecutive days. The monkeys were monitored before and after treatment for 4 months for changes in blood chemistry, hematology, urine, and ocular, neurological, and cardiovascular systems. At the end of the study all animals were sacrificed and gross and microscopic pathological examinations were performed.

Remark : These data indicate that monkeys receiving a total of 108-127g 40% DMSO or equal saline volumes iv during a 9-d study showed no significant or adverse changes in the chemical and physiological parameters studied. No gross or microscopic pathology was found in any monkey at the end of the 4-mo observation period.

Result : The blood chemistries, urinalysis, hematology, and ophtalmologic and gross and histological examinations of tissues in the DMSO animals were not significantly different from those in the control monkey.
The rapid fourfold increase in diuresis over the control values in the monkeys receiving 2 or 3 g/kg DMSO supports previous results. This urine output indicates that DMSO is one of the strongest diuretics known. The absence of any microscopic or gross structural damage to the kidneys

suggests that the coffee-colored urine seen after DMSO administration represents a transient erythrocytic hemolysis, possibly caused by an osmotic gradient due to DMSO in the vascular system. Since this effect was short lived and did not significantly alter the red cell count or the hemoglobin and hematocrit values, we believe the coffee-colored urine represented a transient and reversible condition. It does point out, however, the need to routinely monitor the CBC and hematocrit and hemoglobin whenever DMSO is used in patients at the doses indicated in this study.
The partial thromboplastin time in DMSO treated monkeys decreased from a normal mean of 46 s to a mean of 18.7 s. These values returned to normal when DMSO administration was stopped. Although the PT values in both saline and DMSO treated monkeys fluctuated slightly before and after treatment, the values did not significantly differ from the control standard range. By contrast, the PTT values in both DMSO and saline treated animals were abnormal even before treatments began and remained that way after treatment.
An increase in respiratory rate after DMSO was previously reported. It appears from these studies that DMSO acts as a central respiratory stimulant when given iv in bolus form. A rise in minute respiratory volume concomitant with the rise in respiratory rate was also reported.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
03.06.2003 (39)

Type :
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : inhalation
Exposure period : 6 weeks
Frequency of treatm. : 7 hr/day, 5 days a week for a total 30 exp.
Post exposure period : none
Doses : 0.2 mg/l
Control group : yes, concurrent no treatment
NOAEL : = .2 mg/l
Method : other
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A total of 32 male Sprague-Dawley rats were exposed to 200 mg DMSO per cubic meter of air for 7 hr/day, 5 days a week, for 6 weeks for 30 exposures. Control rats were exposed to a normal chamber environment.
All animals were examined for toxic signs prior to, during, and subsequent to each exposure. These signs included diarrhea, lacrimation, dyspnea, ataxia, anorexia, and unusual behavior. All animals were allowed food and water ad libitum when not being exposed. Body weight was obtained from each animal prior to the first exposure and after the final exposure. Blood was obtained prior to the first exposure and after the final exposure for hematologic evaluation. Hemoglobin concentration, packed erythrocye volume as expressed by the microhematocrit, and total leukocyte and reticulocyte counts were done on all animals

using standard techniques. At the termination of the experiments, all animals were sacrificed with an overdose of a barbitu rate. Blood and tissue specimens were obtained for biochemical analysis, and gross observations of the organs were made. Sections of the heart, lung, liver, spleen, and kidney were taken for histologic examination.

Result : There were no outward toxic signs noted in any of the exposed animals throughout the experimental period of 6 weeks. The characteristic garlic-like odor was detected in the breath of each of the rats after the first day of exposure, and the hair began to appear slightly yellow after the first week. All animals gained weight normally, showing a mean gain of 95.8 % for the test animals and 92.5 % for the controls. No significant alterations were noted in hemoglobin concentrations, microhematocrit, total leukocyte counts, reticulocyte counts, serum glutamic pyruvic and glutamic-oxalo-acetic transaminase activities, liver alkaline phosphatase activity, or liver lactate concentrations.
Gross and histopathologic examinations of organs and tissue were unremarkable except for nonspecific inflammatory changes in the lungs and livers of nearly all animals, including controls.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
Limited hematological, biochemical and histopathological investigations

22.07.2003 (59)

Type :
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 18 months
Frequency of treatm. : daily, 5 days/wk
Post exposure period : none
Doses : 1 - 3 - 9 ml/kg/d (1100 - 3300 - 9900 mg/kg/d)
Control group : yes, concurrent vehicle
NOAEL : = 1100 mg/kg bw
LOAEL : = 9900 mg/kg bw
Method : other: no data
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : A 50% aqueous solution of DMSO was administered by oral gavage daily, 5 days a week for a total of 18 months (78 weeks). Groups of 50 male and 50 female Sprague Dawley rats received daily doses of 1, 3 or 9 ml/kg DMSO; a control group received 9 ml distilled water/kg/day. After 52 weeks, 10 males and 10 females from each were sacrificed. Animals were observed daily, weighed weekly and food intake was calculated at weekly intervals. Ophthalmoscopic examination of the eyes of all animals was made before dosing and then at regular intervals throughout the study. Hematology studies (PCV, hemoglobin, total and differential white cell count and prothrombin index), together with urinalysis and measurement of urine concentration were performed on sample animals from each group after 4, 12, 20, 32, 51, 60 and 72 weeks. After

78 weeks remaining animals were sacrificed and their tissues preserved.

Result : Oral dosing with a 50% aqueous solution of DMSO was continued for a period of 18 months (with an interim sacrifice of some members of each group after one year). Mortalities were few and could not be related to DMSO treatment. Occasional behavioral changes, persisting for about 5 min after dosing, were observed. These consisted of stretching and arching of the back, accompanied by an in-drawing of flanks and abdomen, and were attributed to abdominal discomfort.
Bodyweight records indicated a dose-related depression of weight gain in both sexes, with the exception of males receiving 1 ml/kg (Figures 7 and 8). There was no accompanying reduction of food intake. Laboratory investigations were limited to hematological tests, the only abnormality being a slight r eduction of haemoglobin and PCV in male rats receiving 9 ml/kg.
Examination of the eye revealed no changes in the retira or vitreous. No peripheral (equatorial) opacities were seen and there was no difference in incidence of polar opacities between test and control animals. Prominent nuclear annuli were seen in a small number of animals towards the end of the study, as expected, but there was no dose-relationship to suggest any increase resulting from administration of DMSO. The only relevant finding was some degree of change in the refractive index of the nuclear region in 3 rats receiving 9 ml/kg.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Attached document : Noel Fig 7.bmp
Noel Fig 8.bmp

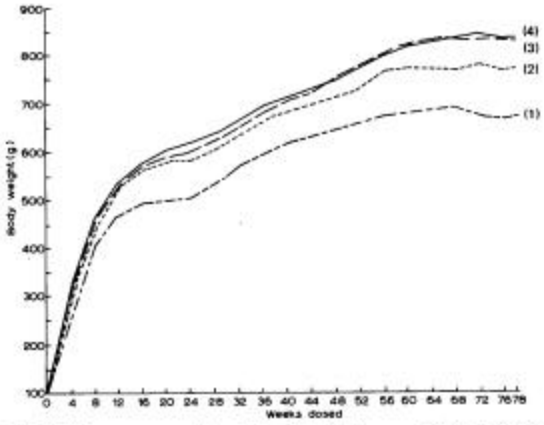

Fig. 7. Weekly group mean bodyweights of male rats. —·—·, Group 1, 9 ml DMSO/kg; ------, Group 2, 3 ml DMSO/kg; — — —, Group 3, 1 ml DMSO/kg; ———, Group 4, Control

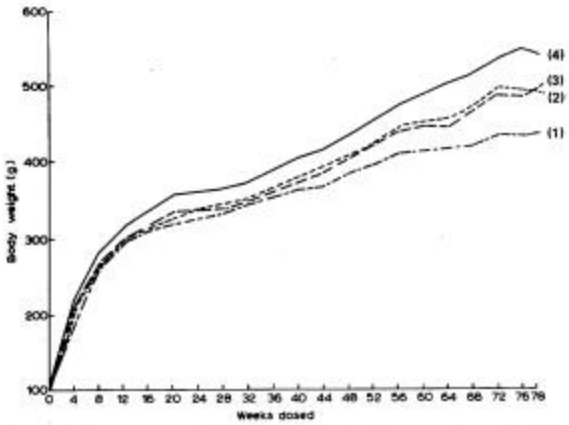

Fig. 8. Weekly group mean bodyweights of female rats. — · — ·, Group 1, 9 ml DMSO/kg; · · · · · ·, Group 2, 3 ml DMSO/kg; — — —, Group 3, 1 ml DMSO/kg; ———, Group 4, Control.

Reliability : (3) invalid
Limited investigation: no blood chemistry and histopathology.

22.07.2003

Type :
Species : mouse
Sex : male/female
Strain : Swiss
Route of admin. : gavage
Exposure period : 3 weeks (5 g/kg), 5 weeks (2.5 g/kg) or 10 weeks (2 g/kg)
Frequency of treatm. : daily, Sunday excepted 6/7 d
Post exposure period : none
Doses : 5, 25.0 2.0 g/kg/day
Control group : yes, concurrent no treatment
LOAEL : = 2000 mg/kg
Method : other: no data
Year : 1969
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : Two mice died at 2 g/kg. Body weight gain was reduced by 20% at 2.5 g/kg and by 21-27% at 5 g/kg.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
24.12.2002 (29)

Type :
Species : mouse
Sex : male/female
Strain : Swiss
Route of admin. : i.p.
Exposure period : 5 weeks
Frequency of treatm. : 6d/week
Post exposure period : none
Doses : 2.5 g/kg/day
Control group : yes, concurrent no treatment
NOAEL : = 2500 mg/kg bw
Method : other: no data
Year : 1969
GLP : no

Test substance : as prescribed by 1.1 - 1.4

Result : Microscopic examination of the tissues in mice revealed that repeated doses of 2.5 g/kg given i.p. causes tubulo nephritis and a more or less diffuse necrosis of the intraperitoneal organs in the area of injection.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid

24.12.2002 (29) (31)

Type :
Species : rabbit
Sex : no data
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 30 days
Frequency of treatm. : daily
Post exposure period : none
Doses : 1.0, 5.0 g/kg
Control group : other: saline
NOAEL : = 1000 mg/kg
LOAEL : = 5000 mg/kg
Method : other
Year : 1971
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Medical grade DMSO was applied daily to the shaved backs of rabbits for 30 days at a dose of 1.0 or 5.0 g/kg/day. Control animals received saline. Blood was drawn by cardiac puncture from each rabbit 1 and 7 days prior to treatment, and on treatment day 1, 7, and 30. Serum chemistry and serum enzyme levels were evaluated. Eye lenses of each rabbit were examined with a biomicroscope before and during treatment. At the end of the study, all rabbits were autopsied and examined for gross pathology.

Result : There was no mortality reported for rabbits receiving daily dermal exposures to DMSO. Application of DMSO at 1 g/kg/day did not induce significant changes in serum chemistry or enzyme levels. Serum LDH levels were elevated in rabbits receiving 5 g/kg/day. There were no gross lesions in DMSO or control animals examined at the end of the study.

Eye lenses from all rabbits were examined. None of the animals treated with 1 g/kg/day displayed lenticular changes. All of the rabbits treated with 5 g/kg/day displayed microscopic changes, which were first detected after 10-15 days treatment. Results were the same in groups of rabbits that received the same doses of DMSO by intraperitoneal injection. Similar lens changes were observed in rabbits which received 5 g/kg/day; no lens changes were seen in the 1 g/kg/day group. Lenticular effects resulting from DMSO treatment appears to be the same regardless of the route of administration, however, the effects are dose dependent.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
Histopathology limited to the eye.

12.08.2003 (155)

Type	:	
Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	90 days
Frequency of treatm.	:	not reported
Post exposure period	:	none
Doses	:	2.2, 4.4, and 8.8 g/kg (as 100 or 50 % solutions)
Control group	:	yes, concurrent vehicle
NOAEL	:	= 2200 mg/kg bw
Method	:	other
Year	:	1967
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Six groups of 2 male and 2 female rabbits received dermal application of 100% DMSO solution at dose levels of 2, 4, and 8 ml/kg or 50% DMSO solution at 4, 8 and 16 ml/kg for 90 days. The rabbits were examined ophthalmoscopically prior to onset of treatment and after 90 days of treatment.
Result	:	Bilateral changes in the ophthalmoscopic appearance of the lens were seen in the two higher dose level groups receiving the 100% DMSO solution and the 50% DMSO solution.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(3) invalid

24.12.2002 (121)

Type	:	
Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	other: dermal to normal and abraded skin
Exposure period	:	22 weeks
Frequency of treatm.	:	5 day/week
Post exposure period	:	none
Doses	:	1.65 and 3 g/kg/d (as 50% or 90% DMSO solutions)
Control group	:	yes, concurrent vehicle
LOAEL	:	= 1650 mg/kg bw
Method	:	other
Year	:	1967
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	50% and 90% solution of DMSO in water were applied 5 days weekly to the skin of 2 series of 5 groups of 6 male and 6 female rabbits (3 months old) at the dose levels of 0, 3 and 9 ml/kg/d. In one series solutions were applied on the intact skin and the other on the abraded skin. The rabbits were examined opthalmoscopically in the 22nd dose-week, slit lamp biomicroscopy was done as well.
Result	:	Lenticular changes were observed in rabbits receiving daily dermal applications of 9 ml/kg, 50% and 90% DMSO, after 15-20 weeks. After 22 weeks these changes were observed in all rabbits receiving 9 ml/kg 90% DMSO and some receiving the smallest dose administered, 3 ml/kg DMSO.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(3) invalid

24.12.2002 (121)

Type	:	
Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	6 months
Frequency of treatm.	:	daily, 5 days a week
Post exposure period	:	12 weeks
Doses	:	1.5, 2.7, 4.5, 8.1 ml/kg/day (1650, 2970, 4950, 8910 mg/kg/day)
Control group	:	other: distilled water
LOAEL	:	= 1650 mg/kg
Method	:	other
Year	:	1975
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : Rabbits received dermal application of DMSO once a day, 5 days a week, to a closely shaven area of approximately 150 sq cm. DMSO was applied as 50% or 90% aqueous solution; volumes applied were equivalent to 1.5, 2,7, 4.5 or 8.1 ml undiluted DMSO per kg. Groups of males and females received daily applications of DMSO to normal and abraded skin. Control animals received distilled water. Treatments continued for 6 months; animals were kept under observation for an additional 12 weeks after treatment was terminated.

Each rabbit was observed daily, weighed weekly and its water consumption was recorded during week 26. Ophthalmoscopic examination was performed on all animals before dosing commenced and then after 5, 8, 14, 20, 22, 28 and 33 weeks. Haematological investigations comprising PCV, haemoglobin, total and differential white cell count, and ESR, were performed initially and at 4, 12, 26 and 32 weeks. At termination, each animal was subjected to a post mortem examination, with subsequent organ weight analysis and histopathology.

Result : Rabbits received dermal applications of DMSO to normal and abraded skin for a period of 23 weeks, when ocular changes were observed. Treatment was withheld from animals showing ocular changes; the remaining animals continued to receive DMSO applications for the scheduled 26 weeks (6 months).

Mortality was high in all groups, however there was no significant differences in mortality between groups.
There were no clinical signs to suggest systemic toxicity.
Local dermal reactions of slight erythema and mild edema were observed following each application. The degree of reaction was similar in all groups. Abrasion of the skin did not increase the reaction. Hair growth was normal and there were no dermal reactions observed during the post-treatment observation interval.

Water consumption, measured during week 26, was markedly increased in animals receiving 8.1 m/kg; a lesser increase in water consumption was noted for other groups receiving DMSO.
Macroscopic and hematological examinations, organ weight analysis, and histopathology did not reveal any adverse effects. There were no changes in dermal morphology except for random occurrences of inflammatory reaction.

Adverse ocular (lenticular) effects were observed. These

were restricted to the lens, and consisted of nuclear refractive changes. There was no effect on the peripheral lens, vitreous humor, or retina. Abrasion of the skin had no effect on the incidence of lenticular effects.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
No blood chemistry analysis. Excepted the eyes, the organs subject to the histopatological examination are not reported.

12.08.2003 (114)

Type :
Species : dog
Sex : male/female
Strain : other: Pembrokeshire Corgis
Route of admin. : gavage
Exposure period : 2 years
Frequency of treatm. : daily, 5 days/wk
Post exposure period : none
Doses : 1; 3; 9 ml/kg (1100 - 3300 - 9900 mg/kg/day)
Control group : other: 1 ml/kg water
LOAEL : = 1100 mg/kg bw
Method : other: no data
Year : 1975
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Dogs were pure-bred Pembrokeshire Corgis obtained at the age of 4-5 months and were assigned to groups; 5 males and 5 females per group. Dogs were dosed orally, once per day for 5 days a week, by gastric intubation with a 50% aqueous solution of DMSO. Groups recieved 9, 3, or 1 ml/kg/day. A control group received 1 ml distilled water/kg/day.

After 18 weeks, unexpected eye changes were observed. Dosing was continued for half the dogs in each group for the remaining 86 weeks; the other half was not treated but observed for signs of recovery. The total interval of dosing was 2 years. Clinical signs were recorded daily; food intake was measured twice daily. All animals were subject to regular examimantion, including ophthalmoscopy. ECG, clinical chemistry, hematology, and urinalysis monitoring was conducted before and at regular intervals during the study.

At the end of the study, all animals were sacrificed and subjected to detailed necropsy. Principal organs were weighed and tissues taken for histopathological examination. Eyes were examined and the lenses removed and weighed; the volume of aqueous humour was measured.

Result : There were no marked clinical signs and only one death occurred, after the 4th dose at the intermediate level. This was caused by accidental inspiration of DMSO, leading to a severe pulmonary reaction; the animal was replaced. Occasional isolated bouts of vomiting were seen at 9 ml/kg/day and transitory "head shaking" was temporarily observed during weeks 11 and 12 at this and the 3 ml/kg/day level.

No adverse effects on bodyweight and food intake were recorded. ECG records were normal throughout except for a

transient, minimal slowing of the heart rate in recordings made after 4 weeks. Terminal radiology of excised bone showed no evidence of osteoporosis.

Laboratory investigations confirmed the persistence of diuresis in dogs receiving 3 ml/kg a nd above (increased "overnight" urine volumes, reduced SG and increased water intake during periods of measurement). No renal damage resulted; normal function was demonstrated by the sensitive urine concentration tests and normal plasma urea levels.

The only other change related to red cells: there were persistently increased PCV and haemoglobin levels, and total red cell count, at 9 ml/kg (Table 1). The red cells had normal haemoglobin concentrations (MCHC) and were of normal size (MCV). Bone marrow examination prior to termination revealed no evidence of toxic changes. It seemed possible that the constant diuresis had resulted in a balance with a slightly higher degree of haemoconcentration than is normally found. No increase in serum proteins could be demonstrated to confirm this possibility.

Ocular effects were observed after 5-10 weeks dosing in the dogs receiving 9 ml/kg including central (nuclear) lenticular changes with alteration of the refractive index (myopia) and by the fifth month, transitory equatorial opacities, central (nuclear) opalescence, and changes in the vitreous humour. Similar effects were observed in dogs receiving 1 and 3 ml/kg but they occurred more slowly.

No abnormalities, other than those in the eye, were detected during macros copic or microscopic examination of organs. The retina was normal. Changes in the lens included an increase in insoluble protein at all dose levels and a reduction of water content in the 3 and 9 ml/kg group. There was a significant reduction of soluble protein and a reduction in glutathione content in the 9 ml/kg group.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Attached document : Noel Table 1.bmp
Noel Table 1 continued.bmp

TABLE I

GROUP MEAN VALUES RELATING TO RED CELLS IN DOGS. (STATISTICAL ANALYSIS: LEAST SIGNIFICANT DIFFERENCES) COMPARED WITH CONTROLS OR SUBSEQUENTLY UNDOSED ANIMALS

Weeks dosed and not dosed	Number of dogs	High		Intermediate		Low		Controls		L.S.D.	
		Dosed	ND	Dosed	ND	Dosed	ND	Dosed	ND	5%[a]	1%[b]
Haemoglobin (g%)											
Pre-dosing (1)	10	11.0		11.0		11.7		11.4			
Pre-dosing (2)	10	12.6		11.8		12.3		11.8			
Pre-dosing (3)	10	13.0		12.1		12.3		12.1			
4 weeks	10	14.8[b]		(13.5)		13.0		13.0		0.90	1.30
12 weeks	10	15.7[b]		(15.2)		15.1		14.1		1.15	1.55
18 weeks	5	17.1[b]		15.5		15.5		14.2		1.18	1.62
24 wks/18 + 6 off	5	19.4[b]	15.5	15.7	15.4	15.3	15.9	15.4	15.3	1.44	1.93
36 wks/18 + 18 off	5	19.3[b]	16.4	16.9	15.3	15.1	15.9	15.3	15.7	2.69	3.63
51 wks/18 + 33 off	5	18.6[b]	16.5	16.2	14.3	14.7	15.3	15.6	15.4	1.68	2.26
65 wks/18 + 47 off	5	16.9	16.6	17.3	15.1	16.3	16.4	17.0	16.0	1.44	1.94
90 wks/18 + 72 off	5	17.2	16.0	16.9	15.7	16.1	17.0	17.1	16.2	1.03	1.39
104 wks/18 + 86 off	5	19.5[b]	16.4	17.5	16.5	16.4	16.5	16.6	15.7	1.75	2.35
Total RBC counts (X 10^6 cells/cmm.)											
Pre-dosing (1)	10	4.33		4.36		4.65		4.37			
Pre-dosing (2)	10	4.88		4.52		4.72		4.68			
Pre-dosing (3)	10	4.92		4.36		4.50		4.32			
4 weeks	10	5.54[b]		(5.19)		4.97		4.99		0.37	0.50
12 weeks	10	6.06[b]		(5.58)		5.65		5.21		0.38	0.49
18 weeks	5	6.03[b]		5.19		5.56		5.07		0.37	0.51
24 wks/18 + 6 off	5	6.46[b]	5.07	5.21	5.17	5.26	5.57	5.36	5.22	0.38	0.51
36 wks/18 + 18 off	5	6.39[b]	5.49	5.73	5.22	5.26	5.60	5.19	5.22	0.45	0.60
51 wks/18 + 33 off	5	6.68[b]	5.95	6.10	5.60	5.52	5.73	5.66	5.75	0.49	0.65
65 wks/18 + 47 off	5	6.27	6.06	6.09	5.79	5.89	6.33	6.15	5.89	0.42	0.56
90 wks/18 + 72 off	5	5.85[b]	5.59	5.83	5.45	5.44	5.74	5.69	5.39	0.43	0.58
104 wks/18 + 86 off	5	6.83[b]	6.09[a]	5.86	5.07	6.14[a]	5.95	5.68	5.43	0.54	0.73

TABLE I (continued)

Weeks dosed and not dosed	Number of dogs	High		Intermediate		Low		Controls		L.S.D.	
		Dosed	ND	Dosed	ND	Dosed	ND	Dosed	ND	5%[a]	1%[b]
Packed cell vol. (% red cells)											
Pre-dosing (1)	10	37		35		38		37			
Pre-dosing (2)	10	39		37		38		37			
Pre-dosing (3)	10	40		37		38		37			
4 weeks	10	46[b]		(42)		41		41		2.69	3.61
12 weeks	10	49[b]		(46)		45		43		3.09	4.14
18 weeks	5	51[b]		47		48		44		3.40	4.69
24 wks/18 + 6 off	5	55[b]	43	47	44	45	46	46	45	4.27	5.75
36 wks/18 + 18 off	5	55[b]	47	49	46	46	47	45	46	3.66	4.92
51 wks/18 + 33 off	5	56[b]	47	50	45	45	49	47	48	4.09	5.51
65 wks/18 + 47 off	5	50	49	51	46	49	51[a]	49	47	3.77	5.07
90 wks/18 + 72 off	5	53[a]	48	50	46	48	50	51	49	3.34	4.49
104 wks/18 + 86 off	5	62[b]	57	56	52	57	56	55	52	5.49	7.38

( ), mean of 9 animals.
ND, not dosed.
L.S.D., least significant differences.
[a] Significant at 5% level.
[b] Significant at 1% level.

Reliability : (3) invalid
The blood chemistry parameters and the organs (excepted the eyes) subject to the histopathological examination are not reported.

26.02.2003

Type :
Species : dog
Sex : male/female
Strain : other: pembrokeshire corgis
Route of admin. : gavage
Exposure period : 132 days
Frequency of treatm. : not reported
Post exposure period : 12 days
Doses : see freetext
Control group : yes, concurrent no treatment
Method : other
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : 3 groups of 10 dogs (young Pembrokeshire Corgis) received a daily oral dose of 4.5 ml/kg for 45 days, then 9 ml/kg; 1.5 ml/kg for 45 days, then 3 ml/kg ; or 0.5 ml/kg for 45 days, then 1 ml/kg DMSO for up to 120 days. Because of changes noted in the group receiving the highest dose level, 5 dogs in this group received non DMSO after the 120th days of treatment.
Result : Lenticular changes were observed in the dogs receiving 4.5 - 9 ml/kg after 68 days. Slight effects were seen in the 0.5 - 1 ml/kg dose group, after 68 days of treatment.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
24.12.2002 (121)

Type :
Species : dog
Sex : male/female
Strain : Beagle
Route of admin. : gavage
Exposure period : 23 weeks
Frequency of treatm. : 5 days a week
Post exposure period : 31 weeks
Doses : 0 - 2500 - 5000 - 10000 - 20000 - 40000 mg/kg/day
Control group : yes, concurrent vehicle
LOAEL : = 2500 mg/kg
Method : other: no data

Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Six pairs (male and female) of young adult beagle dogs received daily oral doses of 0, 2.5, 5, 10, 20 and 40 g/kg/d DMSO, 5 days a week for up to 23 weeks. The 20 and 40 g/kg dose levels were not tolerated by the dogs and were reduced. Administration of DMSO was continued for 23 weeks (107 doses) at which time the DMSO was withdrawn from the seven survivors which were then observed for additional 31 weeks. The dogs were then humanely killes, and histologic examination as performed.
The dogs were examined by indirect and direct ophthalmoscopy under 0.5% tropicamide-induced mydriasis prior to testing and at a minimum of monthly intervals during dosing and after withdrawal.

Result : Changes in the lens of the eye were observed in dogs receiving 5 g/kg after 9 weeks of administration. At lower dose levels by the 18th week all the dogs were affected. Treatment was withheld after 23 weeks and the animals were observed for 31 weeks. The changes persisted after the withdrawal of DMSO but became slightly less pronounced.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
24.12.2002 (121)

Type :
Species : pig
Sex : no data
Strain : no data
Route of admin. : dermal
Exposure period : 123 days
Frequency of treatm. : twice daily
Post exposure period : none
Doses : 825, 1485, 2475 and 4455 mg/kg wb/d
Control group : yes, concurrent vehicle
NOAEL : = 825 mg/kg bw
Method : other
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : 50 and 90% solutions of DMSO in water at the dose levels of 0, 1.5 and 4.5 ml/kg/d were applied twice daily for up to 123 days to the skin of groups of 8 pigs. Ophthalmoscopic examinations were performed on the 90th, 113th and 123rd day of DMSO administration.

Result : Dermal application of 4.5 ml 90 % DMSO/kg twice a day caused lens changes by 90 days of treatment. Lens changes were visible on the 113th day in several of the pigs in the groups receiving 4.5 ml 50% DMSO/kg and 1.5 ml 90% DMSO/kg. No changes were visible in the pigs receiving 1.5 ml 50% DMSO/kg on the 123rd day.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
24.12.2002 (121)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Salmonella typhimurium reverse mutation assay
System of testing : Strains TA97, 98, 100, 102, 104, 1535, 1537, 1538
Test concentration : 100 - 10000 µg per plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: S. typhimurium pre-incubation protocol
Year : 1992
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was tested as a coded chemical in two separate laboratories. Concentrations of DMSO (100, 333, 1000, 3333, and 10,000 ug), overnight culture of S. typhimurium (0.05-0.10 ml), and S-9 mix or buffer were incubated without shaking for 20 minutes. The top agar was added and the contents of the tubes were mixed and poured onto the surfaces of petri dishes. His+ (histidine dependent) colonies arising on plates were machine-counted after two days incubation.

Initial testing was without metabolic activation, with 10% rat liver S-9, or with 10% hamster liver S-9. After a negative result was obtained, DMSO was retested without S-9 and with 30% S-9 from rat and hamster.

Result : DMSO was tested to a maximum test dose of 10 mg/plate, using the Salmonella typhimurium pre-incubation protocol. At least five doses were tested in triplicate; repeat tests were performed after the initial trial. A maximum volume of 0.05 ml was added to each plate.
DMSO was negative, in the presence and absence of metabolic activation, in all eight tester strains.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint

24.12.2002 (158)

Type : Salmonella typhimurium reverse mutation assay
System of testing : Salmonella typhimurium TA 98, 100, 1535, 1537, 1538
Test concentration : up to 500 mg per plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: Ames B.N. et al., Mutat. Res., 31, 347-364, (1975)
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was tested in the standard plate incorporation assay using five S. typhimurium tester strains (TA 98, 100, 1535, 1537, 1538) in the presence and absence of metabolic activation. Multiple geometric dilutions were tested in duplicate plates, starting with the maximum non-toxic dose of 500 mg/plate, with and without rat liverS-9 mix.

Result : DMSO was tested to a maximum test dose of 500 mg per plate. Multiple doses were tested in duplicate.
DMSO was negative, in the presence and absence of metabolic activation, in all strains tested.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.12.2002 (103)

Type : Salmonella typhimurium reverse mutation assay
System of testing : Salmonella typhimurium TA 98, 100, 1535, 1537, 1538
Test concentration : up to 1.4 mM per plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: Ames B.N. et al., Mutat. Res., 31, 347-364, (1975)
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was tested in the standard plate incorporation assay using five S. typhimurium tester strains (TA 98, 100, 1535, 1537, 1538) in the presence and absence of metabolic activation. Multiple geometric dilutions were tested in duplicate plates, starting with the maximum non-toxic dose tested of 1.4 mM, with and without S-9 mix
Result : DMSO was tested to a maximum test dose of 1.4 mM per plate. Multiple doses were tested in duplicate.
DMSO was negative, in the presence and absence of metabolic activation, in all five tester strains.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
24.12.2002 (38)

Type : Salmonella typhimurium reverse mutation assay
System of testing : TA98, TA100, TA1535, TA1537 and TA 1538
Test concentration : up to 5 mg/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: Ames et al, Mut. Res., 1975, 31, 347-364.
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
24.12.2002 (131)

Type : Cytogenetic assay
System of testing : CHO-cells
Test concentration : up to 4990 ug/ml
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473
Year : 1990
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Chinese hamster ovary (CHO) cell cultures were exposed to at

least five concentrations of DMSO, to a maximum concentration of 4990 ug/ml. In tests without metabolic activation, cell cultures were exposed to DMSO for 8 hr. In tests with metabolic activation, cultures were exposed to DMSO and rat liver S-9 for 2 hr. Cell toxicity was determined by comparing cell monolayers in treated flasks with control cultures. Mitotic cells were harvested, treated with hypotonic buffer, and resuspended in fixative. Slides were stained and 200 metaphase cells from each of the top three concentrations were scored for chromosomal aberrations. Chromatid and chromosome gaps were recorded but not used in the analysis. The frequency of polypoid or endoreduplicated cells was also noted.

Result : DMSO was tested in CHO cells to a maximum concentration of 4990 ug/ml. DMSO did not induce cell toxicity or cell cycle delay, and did not induce an increase in the incidence of chromosomal aberrations.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

24.12.2002 (99) (100)

Type : Sister chromatid exchange assay

System of testing : CHO-cells

Test concentration : up to 5000 µg/ml

Cycotoxic concentr. : > 5000 µg/ml

Metabolic activation : with and without

Result : negative

Method : OECD Guide-line 479

Year : 1987

GLP : no data

Test substance : as prescribed by 1.1 - 1.4

Method : Chinese hamster ovary (CHO) cell cultures were exposed to at least five concentrations of DMSO, to a maximum concentration of 5000 ug/ml. In tests without metabolic activation, cell cultures were exposed to DMSO for 24 hr. In tests with metabolic activation, cultures were exposed to DMSO and rat liver S-9 for 2 hr. Cell toxicity was determined by comparing cell monolayers in treated flasks with control cultures. Mitotic cells were harvested, treated with hypotonic buffer, and resuspended in fixative. Slides were stained and 50 second-division M2 cells from each of the top three concentrations were scored for SCEs.

Result : DMSO was tested in CHO cells to a maximum concentration of 5000 ug/ml. DMSO did not induce cell toxicity or cell cycle delay, and did not induce an increase in the incidence of SCEs.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

03.01.2003 (99) (100)

Type : Salmonella typhimurium reverse mutation assay

System of testing : Salmonella typhimurium TA 97, TA 98, TA 100

Test concentration : 100 to 300 mg/plate

Cycotoxic concentr. :

Metabolic activation : with and without

Result : negative

Method : OECD Guide-line 471

Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
05.06.2003 (19)

Type : Salmonella typhimurium reverse mutation assay
System of testing : Samonella typhimurium loci 8AG, Fu, ACA
Test concentration : various (solvent of mutagens)
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: no data
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
05.06.2003 (132)

Type : Gene mutation in Saccharomyces cerevisiae
System of testing : Saccharomyces cerevisiae strain D4 and D5
Test concentration : 1400 mM
Cycotoxic concentr. :
Metabolic activation : without
Result : negative
Method : other
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
05.06.2003 (27)

Type : other: DNA damage + HGPRT locus
System of testing : V 79 cells
Test concentration : 2 mMol
Cycotoxic concentr. :
Metabolic activation : no data
Result : negative
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : Four end points were measured :
the relationships between cell killing, mutation induction and DNA double (dsb) and single (ssb) strand breaks have been studied in V79 cells irradiated with X rays under oxic and anoxic conditions in the presence and in the absence of dimethylsulfoxide (DMSO). Curvilinear relationship were found between all pairs of endpoints, except for dsb versus ssb. Statistical analysis of experimental data has shown that in the absence of DMSO there is evidence of good correlations between cell killing, mutation induction and

dsb in oxic and anoxic conditions. However, when DMSO was present, no significant correlation was found. In the presence of oxygen DMSO always exerts a protective effect while in anoxia it is generally much less protective and induces a strong sensitization with respect to mutation induction. Possibly DMSO acts not only as a radical scavenger but also as an agent inducing chromatin relaxation and/or under anoxia, forming highly mutagenic short term radicals. The present data suggest that lethal and mutational events are at least partially independent and not proportional to the initial number of DNA breaks. This may imply that either other kinds of lesions are involved in cell lethality and mutability, or dose dependent repair mechanisms of dsb have to be considered.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

29.07.2003 (124)

Type : Yeast gene mutation assay
System of testing : Schizosaccharomyces pombe (strain ade6-60/rad10-198,h-)
Test concentration : up to 5% (v/v)
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: Loprieno, N. et al. 1976. Mutat. Res. 40: 317-324.
Year : 1980
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was tested in the S. pombe forward gene mutation assay in the presence and absence of phenobarbitol(PB)-induced mouse liver S-9. Yeast cells were exposed to 0.5, 2.0, 5.0, and 10% (v/v) for 1, 6 and 24 hr.
In a separate experiment, the effect of DMSO on mouse microsomal enzymatic activity was examined in S-10 supernatant from livers of induced and non-induced mice.

Result : Yeast cells exposed to DMSO for 24 hr exhibited 100% mortality; there was no survival at any time interval to cultures exposed to 10% DMSO. Mortality at 1 and 6 hr was dose-related up to a concentration of 5%.
DMSO was consistently negative in the S. pombe forward gene mutation assay, both in the presence and absence of phenobarbitol(PB)-induced mouse liver S-9.
DMSO did not affect the basal or PB-induced microsome-dependent aminopyrine demethylase activity in mouse liver S-10 supernatant.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

29.07.2003 (1)

Type : DNA damage and repair assay
System of testing : UMU gene expression in salmonella typhimurium TA 1535/p SK 1002
Test concentration : 2 to 8 %
Cycotoxic concentr. :
Metabolic activation : without
Result : ambiguous
Method : other: no data
Year : 1990
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : The level of betagalactosidase activity which shows umu expression gene was approximately 3.5 times as high as the background level with 8 % DMSO. The authors reported that DMSO was inactive in the SOS chromotest, essentially similar to the present umu test system. The membrane permeability of DMSO may differ between S. typhimurium in the umu-test and E. Coli in the SOS chromotest. The authors concluded that in any case, further studies are required to elucidate the mechanism of SOS induction by DMSO, justifying our characterisation "Ambiguous results" for this non validated test.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (112)

Type : other: Microscreen prophage-induction assay
System of testing : Escherichia coli WP2s(lambda)
Test concentration : 0.62 to 10.0%
Cycotoxic concentr. :
Metabolic activation : with and without
Result : positive
Method : other: De Marini et al., Env Mol Mut, 1990, 15, 1-9
Year : 1991
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (40)

Type : other: DNA polymerase-deficient mutation assay
System of testing : Escherichia coli
Test concentration : 50 µl/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: Slater et al., Cancer Res., 1971, 31, 970.
Year : 1976
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
24.12.2002 (62)

Type : DNA damage and repair assay
System of testing : Escherichia coli PQ37
Test concentration : 7.8 ng/ml to 7.8 mg/ml
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (19)

Type : other: Mitotic and meiotic chromosome gain in Saccharomyces cerevisiae
System of testing : Saccharomyces cerevisiae BR1669
Test concentration : 16.3 to 52.4 mg/ml
Cycotoxic concentr. :
Metabolic activation : without
Result : negative
Method : other
Year : 1990
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
05.06.2003 (150)

Type : Yeast gene mutation assay
System of testing : Neurospora crassa
Test concentration : N/A see remark
Cycotoxic concentr. :
Metabolic activation : without
Result : negative
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : This paper is a compilation of data found in literature. All results are negative for DMSO.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (4) not assignable
05.06.2003 (22)

Type : other: in vitro micronucleus assay
System of testing : SHE cells
Test concentration : no data
Cycotoxic concentr. :
Metabolic activation : no data
Result : negative
Method : other: Schmuck et al., Mut. Res., 1988, 203,397-404
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
05.06.2003 (63)

Type : Mammalian cell gene mutation assay
System of testing : Mouse lymphoma L5178Y cells, tk-/tk+ assay
Test concentration : 0.74-2.11 M
Cycotoxic concentr. : >= 1.83 M
Metabolic activation : without
Result : negative
Method : other: equivalent to OECD Guide-line 476
Year :
GLP : no data

Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Attached document : Amacher Table1.bmp

Reliability : (3) invalid
Tested only without metabolic activation

05.06.2003 (3)

Type : DNA damage and repair assay
System of testing : primary rat hepatocytes
Test concentration : 0.14 M
Cycotoxic concentr. :
Metabolic activation : without
Result : negative
Method : OECD Guide-line 482
Year : 1989
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
Only one concentration tested

05.06.2003 (153)

Type : Salmonella typhimurium reverse mutation assay
System of testing : Salmonella typhimurium TA100, 1535, 98, 1538, 2637, 1537, 102, 104, 97
Test concentration : 14 to 40 %
Cycotoxic concentr. :
Metabolic activation : with and without
Result : ambiguous
Method : OECD Guide-line 471
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Remark : The concentrations used in this work are unusual.
Mutagenicity of DMSO was induced at very high concentrations, where strong cytotoxicity was observed.
According the authors themselves, DMSO concentrations used in the routine AMES are usually between 7 and 14%.
Therefore they suggest that the routine use of DMSO in bacterial mutagenicity test will not influence the results obtained with test compounds since DMSO concentrations having mutagenic activity (more than about 25 % in strains TA 1537 and TA 2637). These effects are seen with and without S9 mix, after 20 min of incubation.
At a concentration of 33% some lethal toxicity was observed in some strains, and overt toxicity in all strains was observed at 37 and 40%.
Additionally Escherichia coli WP2 and WP2UVRA were used, with the same positive results only in the absence of S9 mix, only after 20 min preincubation, only at 33%

concentration on WP2UVR A. Lethal effects occured in both strains at 40% concentration.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid

29.07.2003 (66)

Type : Mammalian cell gene mutation assay
System of testing : CHO cells, HGPRT assay
Test concentration : 2-16%
Cycotoxic concentr. : >= 10%
Metabolic activation : without
Result : negative
Method : OECD Guide-line 476
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Attached document : DMSO10.bmp

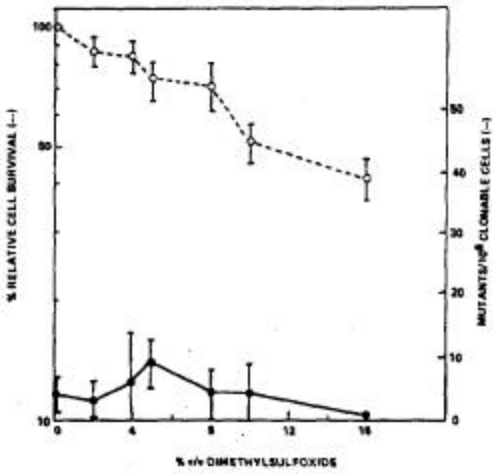

Fig. 2. Mutagenicity and toxicity of dimethyl sulfoxide in CHO cells. Dimethylsulfoxide concentration is indicated as a percent in test medium. Sample means ± 1 S.D. are shown for triplicate trials. The mutant frequency at 5% DMSO was not significantly different than the mutant frequency for solvent controls for $p \leq 0.01$.

Reliability : (3) invalid
Only tested without metabolic activation

03.06.2003

Type : Mammalian cell gene mutation assay
System of testing : Mouse lymphoma L5178Y cells, tk-/tk+ assay
Test concentration : 0.746-1.55 M
Cycotoxic concentr. : >= 1 M
Metabolic activation : without
Result : ambiguous
Method : OECD Guide-line 471
Year : 1988
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Positive at cytotoxic concentrations (>= 1.0 mol/l).
Source : Atofina, Paris-la-Défense, France

Atofina Paris La Défense Cedex

Attached document : Wangenheim table 1.bmp

Test compound	pH	Concentration (mg/l)	Total growth[1]	Mutation frequency[2]	Mutation index[3]
DMSO	[illegible]	0		54	
		0		46	
		0.756	62	42	0.9
		1.008	49	66*	1.4
		1.296	31	77**	1.7
		1.296	16	129***	2.8
		1.556	4	298***	5.5

Reliability : (3) invalid
Only tested without metabolic activation

03.06.2003

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : mouse
Sex : male
Strain : B6C3F1
Route of admin. : i.p.
Exposure period : single
Doses : 5 ml/kg
Result : negative
Method : other: no data
Year : 1989
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was used as solvent in micronucleus test. 3 groups of 8 male B6C3F1 mice received a single intraperitoneal injection of 5 ml/kg DMSO. Bone marrow samples were taken from a single femur of each animal in groups killed at 24, 48 and 72 hours post-injection. Micronucleated cell frequencies were determined by scoring a minimum of 1000 polychromatic erythrocytes for each animal. The ratio of polychromatic to normochromatic cells was determined and was based on the first 100 erythrocytic cells encountered.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
29.07.2003 (104)

Type : Micronucleus assay
Species : other: larvea from Pleurodeles waltl
Sex :
Strain :
Route of admin. : other: dissolved in water of the aquariums
Exposure period : 12 days
Doses : 1100 ppm
Result : negative
Method : other
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions

03.06.2003 (58)

Type : Sister chromatid exchange assay
Species : mouse
Sex : female
Strain : ICR
Route of admin. : i.p.
Exposure period : single on day 13 of gestation
Doses : 2.5, 5.0, 10.0, 20.0 ml/kg
Result : negative
Method : other
Year : 1985
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Sister chromatid exchanges (SCE) and cell replication kinetics (CRK) after maternal DMSO exposure were studied in mouse dams and fetuses. Pregnant ICR-mice had a 55 milligram 5-bromodeoxyuridine (59143) (BrdU) tablet implanted subcutaneously in the abdomen on gestation day 13. After 30 minutes to 1 hour, animals were treated i.p. with 0, 2.5, 5.0 and 10.0 ml/kg DMSO. About 21 hours after BrdU implantation, dams were injected with 80 micrograms colchicine and killed 2 to 3 hours later. Uterine horns and fetuses were removed. Fetal livers and maternal bone marrow were prepared for cell scoring. CRK was assessed by classifying fluorescence plus Giemsa stained metaphase cells as M1, M2, or M3 plus, which indicated one, two, or three more rounds of DNA replication since BrdU treatment, respectively. Average generation time (AGT) as a function of test dose was calculated. SCE was scored as a reciprocal exchange between the chromatids of a chromosome in M2 cells.
Result : There was a significant heterogeneity in relative number of M1, M2, and M3 plus cells among DMSO doses in maternal and fetal cells. DMSO was classified as negative regarding SCE induction in maternal bone marrow and fetal liver.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (2) valid with restrictions

29.07.2003 (130)

Type : Dominant lethal assay
Species : mouse
Sex : male
Strain : Swiss
Route of admin. : i.p.
Exposure period : twice at an interval of 20 hr
Doses : 5000 - 7500 - 10000 mg/kg
Result : negative
Method : other: no data
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 15 male mice were injected intraperitoneally with 5, 7.5, and 10 g/kg DMSO twice at an interval of about 20 hours. Control animals received no treatment. Surviving males were paired with untreated virgin females, which were replaced at weekly intervals for five consecutive weeks. Females were killed and examined for implantion sites and dead implants at 10-11 days after separation from males. Pre-implantation loss was evaluated by comparing the number

of implantation sites in females mated with DMSO-treated males to the number in females mated with untreated males. The incidence of females with dead implantatons was recorded, and pregnancy rates determined.

Result : Male mice treated with DMSO appeared sedated, and consumed less food and water than untreated controls. These effects were dose related and were most apparent in mice that received 10 g/kg DMSO. Incidence of mortality was 7, 20, and 73% for the 5, 7.5 and 10 g/kg groups, respectively. During the first week of matings, pregnancy rates were reduced in females paired with 10 g/kg males. Rates increased in subsequent weeks, and were comparable to controls by week 5. Pregnancy rates of females paired with males given 5 and 7.5 g/kg were similar to controls.
Total implantation rates were reduced in females paired with 7.5 and 10 g/kg males during week 1. There were no significant differences in implantations in subsequent weeks.
The number of dead implantations in females mated to DMSO-treated males did not differ from that of controls during the entire test interval.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

03.06.2003 (35) (101)

Type : other:single-strand breaks in DNA
Species : mouse
Sex : male
Strain : NMRI
Route of admin. : i.p.
Exposure period : single administration
Doses : 25 to 75 mmol/kg (1950 to 5860 mg/kg)
Result : ambiguous
Method : other: Erixon and Ahnström, Mut res, 1979, 59, 257-271
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The method for determination of single-strand breaks (SSB) in DNA by the technique of alkaline unwinding and hydroxylapatite chromatography has been applied for cell nuclei from organs of mice. Male mice were given DMSO by i.p. administration. Cell nuclei were prepared from various organs and then lysed in alkali. The amount of DNA was determined by fluorometry using 4',6-diamidino-2-phenylindole.2HCl. The relative level of SSB in DNA was determined in liver, kidney, lung, spleen, testis or brain, 0.5-24 h after administration of DMSO.

Remark : The highest dose level tested (75 mmol/kg = 5460 mg/kg) is largely in exces of the OECD recommended limit dose (2000 mg/kg) for in vivo genotoxicity testing. The effects observed at this high dose are of doubtful significance.

Result : DMSO induced SSB only in DNA of kidney, 0.5 hr after treatment with the high dose of 75 mmol/kg . No effect was observed in kidney at lower dose levels. No effect as well was obseved in the other organs, 0.5, 4 and 24 after the administration of 0.1 mmol/kg.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

03.06.2003 (147)

Type	:	Drosophila SLRL test
Species	:	Drosophila melanogaster
Sex	:	male
Strain	:	other: Berlin wild males and Basc females
Route of admin.	:	other: intra-abdominal injection
Exposure period	:	Single dose
Doses	:	0.1, 1.0, 5.0% (v/v)
Result	:	negative
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : DMSO was injected intraabdominally into 1-2-day-old males at concentrations of 0.1, 1 and 5%; the volume injected was 0.2 µl per fly. Rod-X and ring-X bearing males were used to test
for sex-linked recessive lethals and for sex chromosome loss, respectively. Controls consisted of males that were not injected, and males that received saline injections. One day after treatment, each male was individually crossed with three 4-day-old virgin females. In order to collect postmeiotic and premeiotic germ cell stages separately, males were mated every two days to a new set of females. Males were mated five times to obtain broods A to E. Mortality and sterility of treated males were recorded during the breeding program.

Result : Increased mortality was observed in all injected males; DMSO did not enhance mortality when compared to saline. Intraabdominal injection of DMSO did not induce sex-linked recessive lethals and did not raise the frequency of sex chromosome loss above the spontaneous level. Data from later broods showed lower frequencies of sex chromosome loss than those from the first brood. This tendency was also observed in untreated controls.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
29.07.2003 (108)

Type	:	Somatic mutation assay
Species	:	Drosophila melanogaster
Sex	:	male/female
Strain	:	other
Route of admin.	:	oral feed
Exposure period	:	2, 8, 24 hr
Doses	:	1% (v/v)
Result	:	negative
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : DMSO was tested in the eye mosaic test which detects genetic recombination in adults as a result of treatment during the larval state. Mutagen-treated Drosophila larvae that are heterozygous for w/wco (white/white-coral) or hemizygous for w/co/Y will display mosaic eye spots as adults. Twin spots represent mitotic recombination, single spots represent somatic mutation as well as mitotic recombination.

Males and females were mated and eggs collected within 4 hr. Larvae were treated at an age of 44 hr after egg deposition, for 2, 8, or 24 hours, by feeding a yeast suspension containing 1% (v/v) DMSO. Larvae were then allowed to continue development and adults were counted and collected one to three days after emergence. Eyes were inspected in paraffin oil under a disecting microscope. Numbers and types of spots were recorded for all mosaic eyes.

Remark : This result agrees with the findings of Mollet that DMSO does not induce sex-link recessive lethals or chromosome loss.

Result : There was no evidence of genetic recombination in the DNA of somatic cells of DMSO-treated Drosophila larvae tested in the eye mosaic test. A similar negative effect was seen in controls.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

29.07.2003 (107)

Type : Somatic mutation assay
Species : Drosophila melanogaster
Sex : male/female
Strain : other
Route of admin. : oral feed
Exposure period : 3 days
Doses : 12.8, 128 mM
Result : negative
Method : other
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was tested in the w/w+ eye mosaic test which detects somatic cell recombination in adults as a result of treatment during the larval stage. The w/w+ system monitors mosaic light spots in the eyes of adult females. Between 12 and 15 pairs of flies were allowed to mate and lay eggs in bottles on food supplemented with 12.8 mM or 128 mM DMSO. Parental flies were discarded and larval feeding with DMSO continued until hatching. Newly hatched females were removed to fresh medium and scored 1-5 days later. Etherized flies were scored under a disecting microscope. Eye spots separated by at least four normal ommatidia were counted as independent events. A minimum of 250 flies were evaluated for each dose tested; at least two separate experiments were conducted at the same dose levels.

Result : There was no evidence of genetic recombination in the DNA of somatic cells of DMSO-treated Drosophila larvae tested in the w/w+ eye mosaic test. A similar negative result was also observed in the parallel control group.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

03.06.2003 (144)

Type : Cytogenetic assay
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : i.p.
Exposure period : 5 administration at 24-hour interval

Doses	:	0.05, 0.5, 2.5, 5 ml/kg
Result	:	positive
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS

Method : Forty albino rats (Sprague-Dawley CD strain from Charles River Breeding Laboratories, Ins., Wilmington, MA) received intraperitoneal (ip) injections of varying concentrations of DMSO for five consecutive days. Each group of 10 rats was administered DMSO at a volume of 5 ml/kg of body weight at concentrations of 1%, 10%, 50%, or 100% DMSO. The DMSO was diluted in distilled water. A vehicle control group of an additional ten animals was treated with distilled water under the same conditions. All rats were 8-10 week old males.
On day six, each animal received an ip injection of colchicine at 2 mg/kg of body weight. Two hours later, animals were sacrificed with CO2 anesthesia followed by cervical dislocation. Immediately after sacrifice, bone marrow was aspirated from both femurs of each rat and placed into 5 ml of prewarmed (37°C) Hank's balanced salt solution. The aspirate was centrifuged for five minutes at 100g. The supernatant was removed, 3.0 ml of 0.075 M KCl was added to each centrifuge tubes, and the tubes were allowed to stand at room temperature for 25 minutes. The cells were centrifuged again for five minutes at 100g. The supernatant was removed and 5 ml ot fixative (3:1 methanol: acetic acid) was added to each precipitate. After 20 minutes at room temperature, the cells were centrifuged as before. The tubes were decanted, and 5 ml of fixative were again added, after which the tubes were sealed and refrigerated overnight at 4°C. Following refrigeration, the cells were centrifuged, decanted, and resuspended in 1-3 ml of fresh fixative.
Three aliquots of the final suspension were dropped onto clean slides which were labeled with the animal number from each respective rat. The slides were allowed to air dry, and were stained for 16 minutes in a preparation of 24 ml Giemsa stock solution, 18 ml acetone, and 198 ml Harleco buffer phosphate (pH 6.8).
Dried slides were held in xylene and subsequently mounted with glass cover slips in Cover Bond mounting media. Three slides were prepared per animal.
The animal number on each slide was covered with masking tape, and each slide was assigned a slide code number. The code was not broken until all slides had been analyzed.
Fifty metaphases per animal were analyzed for chromosome breaks, chromatid breaks, markers, and severely damaged cells. All data were statistically analyzed by the Wilcoxon nonparametric comparison of group means.
A break is defined as any separation that exceeds the width of the chromatid arm, or a discontinuity associated with an unaligned segment of chromosomal material. Chromatid breaks involve only one arm of the chromosome, while chromosomal breaks involve both arms at identical loci. Markers consist of exchanges, rings and dicentrics. An exchange is a shift of a segment of a chromosome to a new position on a nonhomologous chromosome, resulting in altered chromosomal configuration. A ring chromosome is one in which the ends have joined to form a circle. A dicentric chromosome is one

in which two constrictions are symmetrically present on both chromatids. Severely damaged cells are of three types: pulverized cells, cells in which the chromosomes are clumped together so as to render individual chromosomes indistinguishable, and cells showing more than 10 aberrations.

Result : Two animals treated with 1% DMSO and one animal in both the negative control group and the group treated with 100% DMSO did not present analyzable cells. In addition, three animals in the latter group died prior to termination of the study. These events resulted in less than 500 cells analyzed in these three groups.
The percent of aberrant cells per animal increases at each dose level (Table 1). The Wilcoxon nonparametric comparison of group means was performed on the proportion of aberrant cells per animal. All groups treated with DMSO show a statistically significant elevation in chromosome aberrations when compared to the negative control group.
The percent of cells per animal exhibiting each category of chromosome aberration in each group was also compared by the Wilcoxon nonparametric test. The incidence of chromosome breaks is not significantly different between the control and test groups. The level of chromatid breaks is significantly elevated in all test groups except Group 3 (10% DMSO treatment), while the incidence of markers is significantly higher in all test groups when compared to the negative control group. Only in Group 5 is the number of severely damaged cells significantly elevated. The number of severely damaged cells in animals administered 100% DMSO (Group 5) is significantly greater than in all other groups.

Source : Atofina Paris La Défense Cedex

Test substance : Lab Grade-Lot # 35359, J.T. Baker Chemical Co., Phillipsburg, NJ

Attached document : Kapp table 1.tif

Reliability : (2) valid with restrictions

29.07.2003 (85)

Type : other: numerical chromosome aberration study
Species : Drosophila melanogaster
Sex : female
Strain : other
Route of admin. : oral feed
Exposure period : 3 days
Doses : 2%
Result : negative
Method : other
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was fed as a 2% solution to virgin y/y female flies for 3 days. Females were then transferred to regular medium and mated with males to determined the incidence of aneuploidy using the conventional or aneuploidy pattern method. Male and female flies were provided with fresh food after 4 days and removed from food after 6 days. In this way, a (4 + 6) brood pattern was obtained in each of the two DMSO experiments and controls.
-Conventional method: y/y females fed DMSO were mated to normal males (Berlin wild). F1 flies with X-chromosome gain (XXY females) and X-chromosome loss (XO males) are visually distinguished from normal offspring.

-Aneuploidy pattern method: y/y females fed DMSO were mated to C(2L)RM,b;C(2R)RM,vg males. F1 survivors are flies derived from oocytes that aneuploid with respect to chromosome II, eventually in combination with a gain or loss of chromosome I. The number of flies obtained from each brood is examined, and the pattern compared to that obtained from control females.

Remark : DMSO has been consistently negative in Drosophila studies using male germ cells for sex-linked recessive lethals, dominant lethals, somatic mutations, translocations, and ring-X losses. These results demonstrate that DMSO can be used unhesitatingly as a solvent for chemical agents in mutagen screening in Drosophila.

Result : Both the conventional and aneuploidy pattern methods failed to produce evidence that DMSO induces aneuploidy in oocytes of Drosophila melanogaster.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

03.06.2003 (141)

Type : other: Micronucleus assay in bone marrow
Species : mouse
Sex : male
Strain : Swiss
Route of admin. : i.p.
Exposure period : single
Doses : 2 g/kg (as solvent vehicle)
Result : negative
Method : other: Schmid, 1976
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : DMSO was given ip 30 and 6 h to 3 mice before killing. For each mouse, 4 slides were prepared and an average of 4000 polychromatic erythrocytes and the corresponding normochromatic erythrocytes were scored.

Result : DMSO did not affect the incidence of micronuclei, but reduced the P-N ratio slightly (p>0.1).

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
Only 3 mice treated

03.06.2003 (34)

Type : other: Host mediated assay
Species : other: ex vivo in Rodent with Salmonella typhimurium
Sex : no data
Strain :
Route of admin. : other: N/A see remark
Exposure period : see remark
Doses :
Result : negative
Method : other: no data
Year : 1976
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : This paper is a compilation of data without experimental details.

Source : Atofina, Paris-la-Défense, France

Atofina Paris La Défense Cedex
Reliability : (4) not assignable
03.06.2003 (92)

5.7 CARCINOGENICITY

Species : mouse
Sex : female
Strain : other: ICR/Ha swiss
Route of admin. : s.c.
Exposure period : 76 weeks
Frequency of treatm. : once a week
Post exposure period : none
Doses : 0.05 ml/mouse (ca. 1.8 g/kg bw)
Result : negative
Control group : other: 2 groups of 30 mice receiving physiologic saline or water and 120 mice without treatment
Method : other
Year : 1971
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The mice (30) were given weekly sc injection in the left flank of 0.05 ml DMSO. The animals were examined regularly and the finding recorded once a month. The test was continued until there were no survivors. All animals were autopsied, abnormal tissues and tumors were excised and examined histologically.
Result : Median survival time (>76 weeks) was not affected compared to control groups. No benign or malignant tumor was observed at the injection site.
Source : Atofina, Paris-le-Défense, France.
Atofina Paris La Défense Cedex
Reliability : (3) invalid
13.03.2001 (142)

Species : rat
Sex : male/female
Strain : other: wistar adrenal
Route of admin. : s.c.
Exposure period : short term assays
Frequency of treatm. : about number of mitosis
Post exposure period :
Doses : 2.5 and 5 ml/rat
Result :
Control group :
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
24.12.2002 (134)

Species : mouse
Sex : male/female
Strain : other: C3H ventral prostate
Route of admin. : s.c.

Exposure period : short term assays
Frequency of treatm. : about number of mitosis
Post exposure period :
Doses : 0.5 %
Result :
Control group :
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
24.12.2002 (134)

Species : hamster
Sex : male/female
Strain : other: Chinese V79
Route of admin. : s.c.
Exposure period : short term assays
Frequency of treatm. : about number of mitosis
Post exposure period :
Doses : 10 mM
Result :
Control group :
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
24.12.2002 (134)

Species : Syrian hamster
Sex : no data
Strain : other: syrian (embryo)
Route of admin. :
Exposure period : short term assay
Frequency of treatm. :
Post exposure period :
Doses : Concentration 2 % in cell culture embryo or of sternal hyaline cartilage
Result :
Control group : no data specified
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
24.12.2002 (134)

5.8.1 TOXICITY TO FERTILITY

Type : other: reproductive organs toxicity
Species : rat

Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	13 weeks
Frequency of treatm.	:	6 hours/day, 7 days/week
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	13 weeks
No. of generation studies	:	
Doses	:	0.310, 0.964 and 2.783 mg/l
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 2.783 mg/l
Method	:	other: OECD guide-line 413
Year	:	2000
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	During the 90-day inhalation toxicity study reported in section 5.4, the oestrus cycle of female rats was monitored, male rats were subjected to sperm investigations (count, motility and morphology) and the reproductive organs of both sexes were examined histologically.
Result	:	No treatment related effects were observed.
Source	:	Atofina, Paris-le-Défense, France. Atofina Paris La Défense Cedex
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

29.07.2003 (49)

Type	:	Fertility
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	4 days before coï tus
Frequency of treatm.	:	daily
Premating exposure period		
Male	:	4 days
Female	:	4 days
Duration of test	:	until weaning
No. of generation studies	:	
Doses	:	5 g/kg
Control group	:	no data specified
NOAEL parental	:	= 5000 mg/kg bw
NOAEL F1 offspring	:	= 5000 mg/kg bw
Method	:	other
Year	:	1964
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Oral doses of 5 g/kg DMSO administered to male and female rats for 4 days before coï tus did not affect fertility. Female rats treated orally with DMSO throughout gestation delivered normally and the offspring developed normally.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(3) invalid

24.12.2002 (31)

Type	:	Fertility
Species	:	mouse
Sex	:	female
Strain	:	Swiss
Route of admin.	:	other: intraperitoneal or oral (gavage)
Exposure period	:	Different periods of administration during pregnancy (see method)
Frequency of treatm.	:	see method
Premating exposure period		
Male	:	
Female	:	none
Duration of test	:	
No. of generation studies	:	
Doses	:	0.5 ml/kg/g
Control group	:	no
NOAEL parental	:	= 275 mg/kg bw
Method	:	other
Year	:	1982
GLP	:	no data
Test substance	:	other TS: 50/50 mixture of DMSO with 95% ethanol
Method	:	Adult Swiss female mice (25-30 g) were mated with proven Swiss male mice. 0.5 ml/kg/d of a mixture DMSO/95% ethanol 50/50 (v/v) was administered i.p. or p.o. to several groups of pregnant mice as follow: 1. from day 2 through 5 of pregnancy. The laparotomy was performed on day 7 of pregnancy. 2. from day 8 through 12 of pregnancy. The laparotomy was performed on day 18 of pregnancy.
Result	:	1. No inhibition of implantation was observed in mice given an i.p. or p.o dose of 0.5 ml/kg/d of the mixture from GD2 to GD5. 2. No abortifacient effect was observed in pregnant mice given an i.p. or p.o dose of 0.5 ml/kg/d of the mixture from GD8 to GD12.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(3) invalid

29.07.2003 (117)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	10 days, days 6-15 of gestation
Frequency of treatm.	:	daily
Duration of test	:	sacrifice on day 20 of gestation
Doses	:	200 - 1000 - 5000 mg/kg
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1000 mg/kg bw
NOAEL teratogen.	:	= 1000 mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1997
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Three groups of 25 mated female rats received DMSO by gavage at the dose levels of 200, 1000, and 5000 mg/kg/day as a solution in purified water. DMSO was administered each day from day 6 to day 15 of gestation. A control group of 25 mated females was given the vehicle alone. Day 0 of pregnancy was designated as the day of confirmed mating. Clinical signs including mortality and evidence of abortion were checked daily. Food consumption and body weight were recorded at designated intervals during pregnancy.
On day 20 of pregnancy, females were killed. The gravid uterus was weighed and fetuses removed by hysterectormy. Females were examined macroscopically. Litter parameters were recorded: number of corpora lutea, implantation sites, early and late resorptions, and dead and live fetuses. Fetuses were weighed, sexed, and submitted to external examination and then to soft tissue or skeletal examinations.

Result : Maternal data:
There were no clinical signs observed in treated or control groups. No maternal deaths or abortions occurred in any group. Lower food consumption and body weight gain were noted in females of the 5000 mg/kg group. No macroscopic findings were noted at necropsy in any of the females.

Litter data:
Pre- and post-implantation losses were similar in all groups. No treatment-related effects were observed on the number of fetuses or the sex ratio. In the 5000 mg/kg/day group, fetal body weights were slightly lower than that of controls, an indirect consequence, at least in part, of decreased maternal food consumption and body weight gain.

Fetal examination:
No external malformations or anomalies were observed in fetuses from any group. An increased incidence of two soft tissues anomalies were observed: dilated renal pelvis for fetuses in all treated groups, which was associated at 5000 mg/kg/day with an increased incidence of dilated ureter(s). No treatment-related soft tissue malformations were observed. There were no treatment-related skeletal variations or malformations in any group. An increased incidence of reduced or delayed ossification of ribs was observed in fetuses of the 5000 mg/kg group. This skeletal anomaly is considered to be a consequence of the lowered fetal body weights observed for this group. No treatment-related microscopic changes were noted in the kidneys of fetuses with dilated renal pelvis. Dilation of the renal pelvis may be related to the diuretic properties of DMSO.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

24.12.2002 (51)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 10 days, days 6-15 of gestation
Frequency of treatm. : daily

Duration of test	:	sacrifice on day 20 of gestation
Doses	:	1000 - 5000 - 10,000 mg/kg
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1000 mg/kg bw
NOAEL teratogen.	:	= 1000 mg/kg bw
Method	:	other: range-finding study according to OECD guideline 414
Year	:	1996
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : Three groups of seven mated female rats received DMSO by gavage at the dose levels of 1000, 5000, and 10,000 mg/kg/day as a solution in purified water. A constant volume dosage of 10 ml/kg was used for each group. DMSO was administered each day from day 6 to day 15 of gestation. A control group of seven mated females was given the vehicle alone. Day 0 of pregnancy was designated as the day of confirmed mating.
Clinical signs including mortality and evidence of abortion were checked daily. Food consumption and body weight were recorded at designated intervals during pregnancy.
On day 20 of pregnancy, females were killed, examined macroscopically and fetuses removed by Caesarean section. Litter parameters were recorded: number of corpora lutea, implantation sites, resorptions, and dead and live fetuses. Fetuses were weighed, sexed, and submitted to external examination.

Result : Maternal data:
There were no clinical signs observed in treated or control groups. No maternal deaths or abortions occured in any group.
Lower food consumption and body weight gain were noted during treatment (day 6-15 of pregnancy) in females of the 5000 mg/kg group, and throughout the gestation period in females administered 10,000 mg/kg DMSO. No macroscopic findings were noted at necropsy in any of the females of the 1000, 5000, or 10,000 mg/kg DMSO groups.

Litter data:
The mean number of corpora lutea and implantation sites per animal showed some variations between control and treated groups; these differences were not dose related and could not be ascribed to treatment with DMSO. No late resorptions or dead fetuses were noted in any group. Higher rates of early resorptions per animal, and higher total post implantation loss were observed in the 5000 and 10000 mg/kg groups. The mean number of live fetuses per animal presented variations between control and treated groups; these differences were not dose-related and could not be ascribed to treatment with DMSO. A treatment-related decrease in the rate of live fetuses was slightly lower in the 5000 and 10000 mg/kg groups. Slight to moderately lower fetal body weights were noted in the 5000 and 10000 mg/kg groups, in line with the treatment-related effect on maternal food consumption and body weight gain. The sex ratio was similar in control and treated groups.

Fetal examination:
No external anomalies or malformations were observed in fetuses from any group.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (50)

Species : rat
Sex : female
Strain : Wistar
Route of admin. : gavage
Exposure period : d6 to d12 of gestation
Frequency of treatm. : daily
Duration of test : Sacrifice 1 to 3 days before parturition
Doses : 5000 and 10000 mg/kg (as a 50% solution)
Control group : yes, concurrent vehicle
NOAEL teratogen. : = 10000 mg/kg bw
Method : other: no data
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Pregnant rats were administered oral doses of 5 and 10 g/kg/d DMSO on days 6 to 12 of gestation. They were sacrificed 1 to 3 days before parturition. When obtained, the fetuses were weighted, and examined grossly before and after fixing in Bouin's solution.
Result : No effects was observed on the number of females going full term, the number of aborted embryos and the number of malformations.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.
29.07.2003 (30)

Species : rat
Sex : female
Strain : no data
Route of admin. : i.p.
Exposure period : 6-15 post coï tus
Frequency of treatm. : daily
Duration of test : no data
Doses : 2 ml/kg for GD 6 to 15; 2, 4 or 8 ml/kg once or 3 times on GD 5, 7, 9, 11, 13, 15, or 17
Control group : no data specified
NOAEL maternal tox. : < 2000 mg/kg bw
Method : other: no data
Year : 1977
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : When DMSO was administered i.p. to pregnant rats at daily dose of 2 ml/kg for days 6 to 15 of gestation, 2 of 9 dams died and all the fetuses were resorbed completely in the others. When DMSO (2, 4 or 8 ml/kg was administered i.p. either once or 3 times on day 5, 7, 9, 11, 13, 15, or 17 of gestation, increased resorption of foetuses was observed following a dose of 8 ml/kg on day 17, or when DMSO was

administered three times on days 7, 11, or 15.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This study was performed in the 70'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

29.07.2003 (146)

Species : rat
Sex : female
Strain : Wistar
Route of admin. : i.p.
Exposure period : d6 to d12 of gestation
Frequency of treatm. : daily
Duration of test : sacrifice 1 to 3 days before parturition
Doses : 5, 8 and 10 g/kg
Control group : yes, concurrent vehicle
Method : other: no data
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : A dose of 10 g/kg DMSO caused the death of 4 of 14 parent rats and the intraperitoneal injection of 8 to 10 g/kg caused an increase in the number of aborted foetuses, and a reduction in the weight of live foetuses. Eleven out of 729 live foetuses from the rats receiving intraperitoneal doses of DMSO exhibited mal formations (of the abdominal wall,CNS, limbs, jaw and tail), in comparison with 1 out of 558 control foetuses.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

24.12.2002 (30)

Species : mouse
Sex : female
Strain : ICR
Route of admin. : dermal
Exposure period : D9
Frequency of treatm. : single day 9
Duration of test : Day 10 or complete gestation
Doses : concentration in distilled water : 0.04 - 0.4 - 4 %
Control group : yes, concurrent vehicle
Method : other: no data
Year : 1988
GLP : no data
Test substance :

Remark : The dermal application used in this study is not the one recommanded by current guidelines. The lower right appendage of the mice was dipped for 20 seconds into a solution of DMSO.
Result : High frequencies of embryo damages were observed in all DMSO treated group on day 10 of gestation. Litter size determined at birth decreased in the DMSO treated mice.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
29.07.2003 (129)

Species : mouse
Sex : female
Strain : Swiss
Route of admin. : i.p.
Exposure period : d6 to d12 gestation
Frequency of treatm. : daily
Duration of test : sacrifice 1 to 3 days before parturition
Doses : 5, 8, 10 and 12 g/kg
Control group : yes, concurrent vehicle
Method : other: no data
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Pregnant mice were administered daily with intraperitoneal doses of 5 to 12 g/kg DMSO on days 6 to 12 of gestation. Following intraperitoneal administration, 7 out of 100 foetuses showed malformations (4% malformed limbs, 2% anencephalia, 1 % celosomia), compared with 4 malformations out of 1768 control foetuses.
Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.
24.12.2002 (30)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : s.c.
Exposure period : d8, d8 to d9; d8 to d10 of gestation
Frequency of treatm. :
Duration of test : 1 - 2 or 3 days
Doses : 10250 mg/kg
Control group : yes, concurrent no treatment
NOAEL teratogen. : < 10250 mg/kg bw
Method : other: no data
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Subcutaneous injection of 31 rats with 10.25 g DMSO/kg/d on

day 8, 8 and 9, or 8-10 of gestation did not significantly influence the body weight gain of the mothers during pregnancy or of the live young obtained on day 19. DMSO administered on days 8 to 10 of gestation reduced the average number of fetuses per litter and increased the number of resorptions. No gross or skeletal malformations were observed in any of the live fetuses obtained from the DMSO-treated rats.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

29.07.2003 (84)

Species : mouse
Sex : female
Strain : Swiss
Route of admin. : gavage
Exposure period : d6 to d12 of gestation
Frequency of treatm. : daily
Duration of test : Sacrifice 1 to 3 days before parturition
Doses : 5 - 8 - 10 - 12 g/kg
Control group : yes, concurrent vehicle
NOAEL teratogen. : = 12000 mg/kg bw
Method : other: no data
Year : 1967
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Pregnant mice were administered oral doses of 5, 8, 10 and 12 g/kg/d DMSO on days 6 to 12 of gestation, respectively. They were sacrificed 1 to 3 days before parturition. When obtained, the foetuses were weighted, and examined grossly before and after fixing in Bouin's solution.

Remark : Due to many uncertainties on the protocol and the results the absence of statistical analysis and the use of non relevant route of administration and dose levels, this study is not valid to assess the teratogenic potential of DMSO.

Result : No effects was observed on the number of females going full term, the number of aborted embryos and the number of malformations.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

24.12.2002 (30)

Species	:	hamster
Sex	:	female
Strain	:	other: golden
Route of admin.	:	i.p.
Exposure period	:	d8 of gestation
Frequency of treatm.	:	single
Duration of test	:	1 d
Doses	:	0.5 ml per animal (undiluted)
Control group	:	no data specified
NOAEL maternal tox.	:	< 5500 mg/kg bw
NOAEL teratogen.	:	< 5500 mg/kg bw
Method	:	other: no data
Year	:	1966
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Pregnant hamsters were administered a single intraperitoneal injection of 0.5 ml undiluted DMSO on day 8 of gestation and the embryos were examined 1 to 3 days later. DMSO was found to be embryotoxic, the embryocidal effect being most marked in litters from mothers weighing less than 110 g at the time of injection. Various degrees of excencephaly and anencephaly were found in those embryos surviving up to 3 days after the injection.
Source	:	Atofina, Paris-la-Défense, France Atofina Paris La Défense Cedex
Reliability	:	(3) invalid This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

29.07.2003 (57)

Species	:	hamster
Sex	:	female
Strain	:	no data
Route of admin.	:	other: intravenous at doses of 50 to 5500 mg/kg or intraperitoneal at doses of 5500 and 8250 mg/kg
Exposure period	:	on day 8 of gestation
Frequency of treatm.	:	single administration
Duration of test	:	3 days
Doses	:	50 to 8250 mg/kg
Control group	:	yes, historical
NOAEL maternal tox.	:	= 2500 mg/kg bw
NOAEL teratogen.	:	= 2500 mg/kg bw
Method	:	other
Year	:	1966
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 -6 pregnant golden hamsters were injected with dilutions of DMSO ranging from 50 to 5500 mg/kg iv or 5500 and 8250 mg/kg ip on the eighth day of gestation.
Result	:	Examination of the embryos 3 days later revealed that no embryocidal or teratogenic effects were noted until levels of 2500 mg/kg were reached. At higher levels, malformations, including exencephaly, rib fusions, microphthalmia, limb abnormalities and cleft lip were found. There was no

appreciable effect of DMSO on maternal weight gain or health.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid

24.12.2002 (56)

Species : rabbit
Sex : female
Strain : other
Route of admin. : s.c.
Exposure period : 6 to 14d of gestation
Frequency of treatm. : daily
Duration of test : GD 20 to GD 24
Doses : 4 g/kg
Control group : yes, concurrent vehicle
NOAEL teratogen. : = 4000 mg/kg bw
Method : other: no data
Year : 1967
GLP :
Test substance :

Remark : Five pregnant rabbits received a daily subcutaneous dose of 4
g/kg DMSO on days 6 to 14 of gestation. There were no adverse effects upon fetal weight or numbers.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

29.07.2003 (30)

Species : rabbit
Sex : female
Strain : other
Route of admin. : gavage
Exposure period : day 6 to 14 of gestation
Frequency of treatm. : daily
Duration of test : sacrifice on GD 20 to GD 24
Doses : 5 g/kg
Control group : yes, concurrent vehicle
NOAEL teratogen. : = 5000 mg/kg bw
Method : other: no data
Year : 1967
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : 10 pregnant rabbits received a daily oral dose of 5 g/kg DMSO
(as a 50% solution) on days 6 to 14 of gestation. the rabbits were sacrificed on GD20 to 24.

Remark : Due to many uncertainties on the protocol and the results this study is not valid to assess the teratogenic potential of DMSO.

Result : There were no adverse effects upon fetal weight, numbers or

malformations.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

29.07.2003 (30)

Species : hen
Sex :
Strain : Leghorn
Route of admin. : other: injection
Exposure period : day 3 of incubation
Frequency of treatm. : single between stages 17 and 23
Duration of test : eggs are allowed to grow to day 10 of incubation
Doses : 1µl 90 % DMSO
Control group : yes, concurrent no treatment
Method : other: no data
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Result : Mortality was not significantly different between DMSO-treated and untreated embryos. Statistical analysis and histological data suggest that scapular and vertebral defects were caused by DMSO induced damage to somites.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This positive result is questionable due to the non validated model used.

24.12.2002 (90)

Species : hen
Sex : no data
Strain : other: Rhode island
Route of admin. : other: injection
Exposure period : days 3 or 4 of incubation
Frequency of treatm. : single
Duration of test :
Doses : solutions containing 50 % DMSO
Control group : yes, concurrent vehicle
Method : other
Year : 1965
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : Positive result is questionnable due to the non validated model and the high concentration used.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental

conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

24.12.2002 (32)

Species : rabbit
Sex : female
Strain : other
Route of admin. : s.c.
Exposure period : whole pregnancy
Frequency of treatm. : daily
Duration of test :
Doses : 2000 and 4000 mg/kg
Control group : yes, concurrent no treatment
NOAEL teratogen. : = 4000 mg/kg bw
Method : other: no data
Year : 1965
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex
Reliability : (3) invalid
This study was performed in the early 60'. Protocols of teratogenic studies were not validated. Insufficient number of animal, without S.P.F. status, doubtful breeding (feeding - environmental status) were used. In these experimental conditions, it is difficult to find out the precise results in the papers, and it is impossible to interpretate (no statistical evaluation on unformal findings). These studies are not valid to assess the teratogenic potential of DMSO.

24.12.2002 (32)

Species : other: Xenopus laevis (South African clawed frog)
Sex : male/female
Strain : other: FETAX assay
Route of admin. : other: immersion
Exposure period : 96 hr
Frequency of treatm. : continuous
Duration of test : 96 hr
Doses : .25, .5, .75. 1.0, 1.25. 1.5, 1.75, 2.0 % (v/v)
Control group : yes, concurrent no treatment
NOAEL teratogen. : = 1 %
Method : other: FETAX assay
Year : 1992
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The Frog Embryo Teratogenesis Assay-Xenopus (FETAX) assay was used to assess the teratogenic potential of DMSO. Embryos of the South African clawed frog were exposed for 96 hr to DMSO at dose levels of 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, and 1.75% (v/v). Exposure groups of embryos were maintained using a static renewal system in which exposure media was changed at 24-hr intervals. Control embryos were reared in FETAX solution under identical environmental conditions. A total of 200 embryos were tested per concentration. Survival was monitored at 24-hr intervals. Length, as an indicator of growth effects, and developmental malformations were determined at the end of the 96-hr assay. The 96hr LC50, 96 hr EC50 for malformations, and the NOEL

for mortality, malformation, and growth were also determined.

Remark : Xenopus embryos were able to survive and develop normally in relatively high concentrations of DMSO. The estimated NOELs are 1.0% for malformations, 1.50 - 1.75% for mortality, and 1.0 - 1.25% for growth. The estimated TIs (teratogenic index) for DMSO of 1.20 - 1.24 indicate that DMSO should be designated as having a low teratogenic potential in Xenopus. This classification is comparable to mammalian and avian studies which concluded that DMSO is generally non-teratogenic.

Result : There was a marked increase in embryo mortality at the top dose concentration of 2.0%. The LC50 for replicate experiments was 1.92%. A dose-dependent increase in malformations was observed. The EC50 for malformations was 1.57%. Malformations observed included skeletal anomalies, ocular abnormalities, and gut abnormalities. The frequency of these malformations increased with increasing concentrations. Abnormal swimming behavior, characterized by swimming in a spiral, and decreased growth, were also observed at concentrations at or greater than 1.0%.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

24.12.2002 (47)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Type of experience : Human

Method : The absorption, excretion and metabolism of DMSO have been studied in man by gas chromatography and radiometric techniques. DMSO was administered orally at a dose of 1g/kg as a 70% aqueous solution; a dose of 1 g/kg was administered dermally.

Remark : DMSO was readily absorbed when administered dermally, peak serum levels occurring after 4 -8 hr. Orally administered DMSO was rapidly absorbed, reaching a peak serum level in 4 hr. Serum levels of DMSO were undetectable after 120 hr. Both unchanged DMSO and a metabolite, dimethylsulfone (DMSO2) were isolated from urine. Dimethylsulfone appeared in serum after about 48 hr and persisted for as long as 400 hr. Urinary excretion of DMSO after dermal and oral administration amounted to approximately 13% and 30-68% of the dose, respectively. Excretion of DMSO2 was about 5 to 10% and 21 to 23%, respectively. Data for subjects given DMSO chronically are also presented in this publication, as is evidence that the fraction of DMSO excreted is entirely accounted for by unchanged DMSO and DMSO2.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions

27.12.2002 (76)

Type of experience : Human

Remark : In man, DMSO is oxidized into dimethylsulfone DMSO2, metabolite excreted by urine (17-22 %). DMSO is reduced into dimethylsulfide, DMS, a volatile metabolite, responsible for garlic odour of exhaled air (1 %). About 85 % is excreted unchanged, both by urine (50 %) and feces (50 %). The half time for elimination in volunteers given 1000 mg/kg intravenously is 4 days. By oral route, the same dose is excreted about 51 % as DMSO and about 10 % DMSO2 in urine within 120 hrs.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
24.12.2002 (118)

Type of experience : Human

Method : Plasma concentrations of DMSO, dimethylsulfone (DMSO2), and dimethylsufide (DMS) were assessed in 10 patients who underwent autologous transplants with stem cells, cryopreserved in 10% DMSO (vol/vol). Blood was sampled at multiple times after the stem-cell infusion. Urine was pooled during the 24 hours postinfusion. DMSO, DMSO2, and DMS were assayed simultaneously by gas chromatography. A one-compartment model with saturable elimination proved most suitable for fitting plasma DMSO concentration versus time data.

Result : Stem-cell volumes infused ranged between 180 and 585 ml. (254 to 824 mmol DMSO). Infusions lasted between 20 and 120 minutes. Peak plasma DMSO concentrations were 19.1 ± 6.3 mmol/L. Pharmacokinetic parameters for volume of the central compartment (Vc), maximum velocity (Vmax), and Michaels-Menten constant (Km) were 37.3 ± 17 L, 0.99 ± 0.57 mmol/L/h, and 5.2 ± 5.0 mmol/L, respectively. Plasma DMS02 concentrations increased during the first 24 hours, plateaued at 4.4 ± 1.2 mmol/L, and remained there until 48 hours (the last sample). DMS concentrations were at steady-state by 5 minutes and remained between 3 and 5 mmol/L for 48 hours. Urinary excretion of DMSO and DMS02 accounted for 44% ± 4% and 4% ± 1%, respectively, of the administered DMSO dose. Renal clearance of DMSO was 14.1± 3.4 ml/min.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
29.07.2003 (48)

Type of experience : Human

Remark : Adverse effect: dermal and ocular application
In humans, topical and intradermal application of DMSO produced garlic breath, mast cell degranulation, an increase in polymorphonuclear leukocytes and perivascular eosinophils, itching, and histamine mediated and non histamine dependent whealing and erythematous flare. Two drops of >50% DMSO in the eye caused a temporary burning sensation and vasodilatation; concentrations of <50% exhibited no effects.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
24.12.2002 (152)

Type of experience : Human

Remark : Adverse effect: skin irritation
Dermal exposure to DMSO causes skin reactions, erythema and pruritis, which appear immediately after contact with the undiluted substance; 70% solutions are usually tolerated without symptoms. In very sensitive individuals, however, reactions have been seen after contact with 10% solutions. The skin reaction to the undiluted substance is ascribed to the hygroscopic properties of DMSO, on the one hand, and to the exothermic dissolving process on the other.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
24.12.2002 (120)

Type of experience : Human - Medical Data

Remark : Adverse effect: intravenous administration
Yellowlees et al. and Greenfield reported a toxic reaction in two elderly people receiving DMSO intravenously for treatment of arthritis (three daily doses of 100 g of 20 % DMSO). In one patient there was serious illness including oliguria, hemolysis, tremor, and loss of consciousness. The second patient did not become ill. Both patients had changes in blood aspartate transaminase, hydroxy-butyrate dehydrogenase, and creatine kinase, and elevation of blood creatinine and urea nitrogen. Prothrombin and partial thromboplastin times were significantly shorter.

Knott and van Rijswijk, who had treated patients similarly to Yellowlees et al but without toxic effect, suggest that the toxic reactions seen in the latter's patients were caused by the action of DMSO as a drug potentiator, and that the reaction may have been due to an enhancement of the toxicity of quinine sulfate, indomethacin, or phenothiazine, which patients were receiving at the time.
Another patient receiving intravenously cryopreserved autologous marrow blood (to which DMSO was added) for treatment of myeloblastic leukemia suffered a reaction to the administration. In addition to a DMOP in hemoglobin, the patient became agitated, pyrexic, hypotensive, and developed tachycardia. Recovery occured but the patient died ten days later. O'Dommell et al believed the mixture was toxic (the patient received 35g of DMSO as a 10% solution), and suggested that DMSO interactions may be significant and potentially dangerous. These doses are considerable.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
29.07.2003 (120)

Type of experience : Human - Medical Data

Remark : A 43-y-old Caucasian female applied DMSO to her lower abdomen for treatment of interstitial cystitis. She used 2 treatments separated by 1 1/2 h consisting of applications of 2 ounces of DMSO mixed with 2 ounces of distilled water on a clean white washcloth over a 6" x 12" skin area, for a

total application of 132 g or 1.8 g/kg. The first application was from a bottle obtained from a family member and had been used by the family member with no reported ill effects. The bottle came from a store that sold undiluted DMSO. After the first application the patient experienced a garlic taste in her mouth, but had no improvement in her abdominal pain. The second application was from a previously unopened bottle from the same store; a pulverized 200 mg ibuprofen tablet was mixed into the solution. She again noted a garlic taste but no symptomatic improvement.

Within 24 h the patient developed fatigue and cyanosis, as well as dyspnea with mild exertion which did not worsen over time. She sought medical attention for her symptoms 10 d after the DMSO application and presented to the doctor's office with generalized cyanosis and a room air pulse oximetry of 42-47%. She was mildly dyspneic but fully alert. She was transferred to the emergency department where her oximetry increased to 54% on oxygen per nasal cannula. On admission she reported her current medications as docusate calcium, ibuprofen, amitriptyline, pseudoephedrine, valaciclovir, loratadine, guaifenesin, azelastine nasal spray, and "Yeast Fighters", in over-the-counter preparation containing lactobacillus acidophilus bacteria, all of which she had been taking regularly for several months prior to admission. In addition, she had taken lansoprazole for approximately 2 w, starting 11 d prior to onset of the cyanosis, alprazolam for a longer period on an as needed basis, and 200 mg phenazopyridine tid starting 3 d after the onset of cyanosis.

Her initial laboratory tests were remarkable for a 47% methemoglobin level on an Instrumentation Laboratory carbon monoxide-oximeter model 282, a hemoglobin of 9.4 g/dl, a hematocrit of 27.7%, and a reticulocyte count of 5.9%. She received 2 treatments with 1 mg methylene blue/kg iv without significant improvement in either her cyanosis or methemoglobin level. Repeat analysis on a blood sample drawn the day following admission using a Radiometer OSM-3 carbon monoxide-oximeter demonstrated a sulfhemoglobin level of 6.2% and a methemoglobin level of < 0.1%. During hospitalization the patient was transfused with 2 units of packed red blood cells. She was discharged on the third hospital day still on oxygen but with continued symptomatic improvement. Her G6PD level was 280 U/ trillion RBC (normal range 146-376).

Analysis of the DMSO solution from the second bottle did not reveal any contaminants. The first bottle of DMSO had been discarded and was not available for analysis.
Adverse effect: Sulhemoglobinemia after dermal exposure

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

24.12.2002 (26)

Type of experience : Human - Medical Data

Method : Male volunteer subjects, ages 21-55, were treated with DMSO, applied as an 80% gel, to the skin in a single daily dose of 1 g/kg body weight. DMSO was applied daily for 12 weeks; a total of 38 subjects completed the entire study. A control group of 18 males, not exposed to DMSO, were studied in a

similar manner. Physical and laboratory examinations were performed prior to the start of the study. Blood and urine were obtained from all subjects at 1,2,4,6,8,and 13 weeks. All subjects received a physical examination at the end of the study. All subjects were given ophthalmological examinations prior to initiation of the study, at weekly intervals during the study, and at intervals up to 18 months after treatment was terminated.

Remark : Clinical study: dermal exposure and effects on eye

Result : Subjects treated with DMSO exhibited a characteristic respiratory odor, previously identified as dimethyl sulfide, a metabolite. A variable degree of skin reaction was observed, characterized by wheal and erythema, drying and scaling. Other side effects included some sedation, and occasional bouts of insomnia and nausea.
With the exception of eosinophilia, no significant abnormalities were observed in blood chemistry, hematology, and urine analysis. DMSO had no significant effect on pulmonary function, EKG or EEG.
Subjective eye complaints consisted of mild photophobia and foreign body sensations. Less frequently, tearing, blurring of vision, disturbances in peripheral vision, and tiring of the eyes were mentioned. These symptoms could not be substantiated by ophthalmological examination or testing and did not persist after DMSO was discontinued. There were no differences in accommodation, near point of convergence, ocular tension, cycloplegic retinoscopy, and cycloplegic refraction. Slit lamp examination revealed no abnormal corneal or lens changes. Visual function, and pupillary mydriasis to 1% tropicamide were not altered.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (21) (77)

Type of experience : Human - Medical Data

Remark : Clinical study: skin sensitization
No skin sensitization reaction was observed in 23 subjects after five 48-hour induction exposures to 75% DMSO solution (each one preceded by a 24-hour pre-treatment with 5% sodium lauryl sulphate) and challenge with 25% DMSO solution.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (88)

Type of experience : Human - Medical Data

Remark : Clinical study: effects on the renal function
DMSO administered intravenously can protect experimental animals with massive stroke and brain swelling from mortality and neurologic impairment. Studies in patients suffering from cerebral trauma also suggest considerable efficacy. Intravenous DMSO was used to treat seven patients with stable spinal cord injuries. Because of drug-associated hemoglobinemia and hemoglobinuria, the patients were studied for subtle evidence of renal tubular dysfunction by serial measurements of urinary beta-2-microglobin excretion. No increases in tubular protein excretion or decreases in glomerular filtration rate were observed following short-term infusions of 10-40% DMSO. No significant

short-term nephrotoxicity was observed from intravenous DMSO.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (9)

5.11 ADDITIONAL REMARKS

Type : Distribution

Remark : A. Membrane penetration
In man radioactivity of 35S DMSO appeared in blood 5 min after cutaneous application. One hour later, radioactivity could detected in bones. This readily crossing depends on a reversible configuration change of the skin proteinic barrier occuring when DMSO substitutes for water.
B. Membrane transport
DMSO carry a wide range of substances through living membranes, vegetal or animal. Concentration of active substance in DMSO are 0.5 to 90 %. Concentrations above 10 % can be IRRITATING for skin by repeated application.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
27.12.2002 (79)

Type : Biochemical or cellular interactions

Remark : Dimethyl sulphoxide (DMSO), at concentrations of 1-2%, induces terminal differentiation in several different cell types in vitro and enhances the growth of newborn mouse epidermal cells in primary culture under conditions that also permit terminal differentiation. We have found that DMSO concentrations approaching 4 % reversibly inhibited (with little overt toxicity) terminal differentiation of normal epidermal cells from newborn SENCAR mice. Cells cultured in medium containing 4 % DMSO and calcium in excess of 1 mM did not stratify extensively or slough large numbers of squamous cells or keratin bundles, as revealed by light and electron microscopy. The number of detergent insoluble cornified envelopes was similarly reduced. Long term growth of epidermal colonies in secondary culture was optimum in 1% DMSO, this concentration also permitting normal terminal differentiation of these cells. Since DMSO had these effects on epidermal cells in vitro, it may also affect epidermal cell proliferation and terminal differentiation in vivo, an important consideration should DMSO ever be approved for topical use in the US.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
12.09.2000 (105)

Type : Biochemical or cellular interactions

Remark : Dimethyl sulfoxide (DMSO) can protect the liver from injury produced by a variety of hepatotoxicants when administered prior to or concomitant with the toxicants. This protective action has previously been attributed to DMSO-induced

inhibition of bioactivation of the compounds to toxic intermediates. In these studi es, the ability of DMSO to provide protection when administered 10 hr after a toxicant was evaluated in several animal models of xenobiotic-induced liver and kidney injury.

In the guinea pig model of halothane-associated hepatotoxicity, male outbred Hartley guinea pigs received 2 ml/kg DMSO 10 hr after an inhalation exposure to 1.0% halothane, 40% O2 for 4 hr. DMSO decreased the extent of liver necrosis as indicated by a threefold decrease in plasma alanine aminotransferase activity 48 hr after exposure and a reduction in the incidence and extent of zone 3 necrosis. These results do not appear to be due to alterations in halothane biotransformation since DMSO administered at 10 hr after halothane had no affect on plasma concentrations of the halothane metabolite trifluoroacetic acid or covalent binding by reactive halothane biotransformation intermediates to hepatic protein. In addition, administration of the structurally analogous biotransformation inhibitor diallyl sulfide at 10 hr after halothane also had no effect on biotransformation or covalent binding but provided no protection from liver injury. Hepatic glutathione concentrations in the guinea pigs 24 hr after halothane exposure were also unaffected by late treatment with DMSO. Further studies in male Sprague-Dawley rats demonstrated the abilitv of DMSO to decrease the hepatic injury resulting from oral administration of 1.0 ml/kg chloroform or 0.5 ml/kg bromobenzene when administered 10 hr after either toxicant. The chloroform-treated rats also developed renal tubular necrosis with large increases in plasma creatinine and urea nitrogen, which were completely ameliorated by DMSO.

Elucidating the mechanism(s) of this protective action of late DMSO administration should provide insight into the cascade of events that lead to liver and kidney injury from toxicants and, hopefully, therapeutic modalities for individuals suffering from acute, progressing, xenobiotic-induced hepatitis.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
29.07.2003 (95)

Type : Biochemical or cellular interactions

Method : DMSO has previously been shown to attenuate chloroform (CHCl3) and bromobenzene (BB) induced hepatotoxicity in the rat when a dose of 2.0 ml/kg is given 24 hr after the toxicants (Lind and Gandolfi, 1997). However, the optimal dose of DMSO and the latest time at which DMSO can be administered and still provide effective protection have not been determined. In order to determine the latest time at which DMSO can interrupt the development of necrosis, male Sprague-Dawley rats received either 0.75 ml/kg CHCl3 or 0.5 ml/kg BB, 20 % in corn oil, po, followed by single dose of 2 ml/kg DMSO, 50 % in saline, ip, at 24, 26, 28 or 30 hr later. Positive control groups received either CHCl3 or BB and then 4.0 ml/kg saline, ip, 24 hr later. All of the animals were then killed 48 hr after toxicant dosing. The extent of liver injury present when DMSO was administered

was examined by killing animals at 24, 26, 28 or 30 hr after toxicant dosing. The optimal dose of DMSO for providing protection was estimated by administering either 0, 1.0, 2.0, 3.0 or 4.0 ml/kg DMSO at 24 hr after toxicant dosing and then killing the animals at 48 hr.

Result : Delaying DMSO administration to times later than 24 hr after toxicant dosing led to a loss of protection as indicated by both plasma ALT activity and the light microscopic appearance of liver tissue. The distinctive liver lesions present at 24 hr after CHCl3 or BB dosing rapidly expanded from being limited around central veins to bridging between centrilobular areas in only a few hours. This was accompanied by large increases in plasma ALT. With both toxicants, doses of DMSO greater than 2 ml/kg did not enhance its protective action while the lower dose of 1 ml/kg DMSO was not as effective. The loss of DMSO's antidotal action when given at times later than 24 hr after the toxicants indicates irreversible changes were underway as the centrilobular lesions progressed from being limited to more bridging in nature.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
12.09.2000 (96)

Type : Immunotoxicity

Method : Male C3H/HeJ mice weighing between 20-30 g were used. In experiments requiring a comparison between two groups of animals (i.e., DMSO-treated vs. untreated), care was taken to match all groups relative to their whole body weight prior to the start of DMSO treatment and/or antigen injection. DMSO was mixed with tap water and mice were allowed to drink ad libitum. In a separate study, intraperitoneally administered DMSO was given in undiluted daily injections of 0.1 or 0.2ml.
Immunization of mice was accomplished by a single intraperitoneal injection (0.1 ml) of 10% sheep red blood cells suspended in sterile saline.
The serum levels of IgM, IgG1, IgG2a, IgG2e, and IgA were determined by radial diffusion assays using commercially, prepared assay kits and reference.
The number of direct (IgM) and facilitated (IgG1, IgG2b, and IgA) plaques were evaluated for spleen cell suspensions using the microtechnique. Each serum was titrated for hemagglutination. Total body weights and spleen weights were measured and the percent of the spleen weight to whole body weight was calculated.

Remark : The effects observed at high dose of DMSO, 5% in the drinking water (equivalent to a daily intake of 27 g/kg during the first week to 52 g/kg by the end of the third week), or 0.1 and 0.2 ml/animal by ip injection (equivalent to 5 and 10 g/kg, respectively) should be interpreted with caution taken into account the huge amount of DMSO administered.

Result : The general effects of oral DMSO were first evaluated in normal uninjected animals. Age- and weight-matched mice were separated into four groups of 35 each (5 mice/cage) and given 1%, 2.5%, 5%, or 10% DMSO (V/V) in their drinking water. A fifth group served as controls and received ordinary tap water. All animals were allowed to drink ad libitum. The amount of food and water consumed were measured

daily for six weeks. Mice refused to drink 10% DMSO and were eliminated from the study. By the 4th week, mice drinking 5% and 2.5% DMSO had increased daily fluid intake from 5.5 ml/day/mouse (controls) to 23.5 ml/day/mouse and 10 ml/day/mouse, respectively. No difference was observed for the amount of food consumed when mice drinking 5% DMSO were compared with controls. During the six-week period, mice drinking 5% DMSO experienced a significant weight loss for both total body weight and spleen weight. The percent of spleen weight to total body weight also dropped significantly. No histological differences between controls and DMSO-treated mice were noted when stained paraffin sections of spleen, lung, kidney, liver, gut, and lymph nodes from the two groups were compared. Total serum volume, determined from hematocrit values, had dropped by 20% (P > .001) in the fourth week of 5% DMSO treatment. By the sixth week of treatment, however, the difference in serum volume was only 10% (P > 0.01).
Although an occasional test group revealed slightly elevated values for individual immunoglobulin classes, differences between treated and untreated animals were not significant.
In a second study, the effect of intraperitoneal DMSO on serum immunoglobulin levels was evaluated for matched groups of 10 animals given daily intraperitoneal injections of 0.1 or 0.2 ml of undiluted DMSO. Alter three injections of 0.2 ml, only six animais survived and immunoglobulin concentrations were determined on the fourth day. Animals given 0.1 ml received 7 daily injections and their serum immunoglobulin levels were assayed on the 8th day. Surviving animals given 0.2 ml DMSO (8.8g/kg) demonstrated a 60-80% drop in IgG subclasses, a 64% drop in IgA, and a 50% drop in IgM. Animals given 0.1 ml (4.4g/kg) experienced a 30% drop for IgG subclasses and a 21% drop for IgA. IgM levels remained unchanged.
The primary humoral immune response was evaluated in two groups of 25 mice allowed to drink 5% DMSO ad libitum for 16 days or 8 weeks prior to (and during) the 7-day immunization period. The results were compared with an untreated control group of 25 similarly immunized mice. Five animals from each group were evaluated for PFCs, immunoglobulin concentrations, and hemagglutination titers on days 3-7 after SRBC injection. An additional 30 mice were included in both the 16 day pre-DMSO groups and controls for comparison of hemagglutination titers at 10-14 and 38 days after immunization. All three groups demonstrated an increase in spleen size measured on days 3, 4, and 5 after antigen injection. Spleens from DMSO-treated animals, however, remained significantly smaller than those of the untreated controls. On the basis of plaque-forming cells measured 3-7 days after antigen injection, DMSO-treated mice experienced inhibition of IgM on days 3, 4, and 5, IgG(s) on days 4, 5, and 6, and IgA on day 4 (and day 5 for 8-week DMSO group). This difference was further reflected in the hemagglutination titers, which were significantly lower in the treated population. Immunoglobulin levels were assayed daily 3-7 days after injection. Except for serum IgG, differences in immunoglobulin levels were not significant. When the two DMSO-treated groups were compared, plaque-forming cells and hemagglutination titers were significantly lower in mice having ingested DMSO for 8 weeks prior to immunization. The increased inhibition was also reflected by a 24-hr delay in the peak responsiveness of

plaque-forming cells. No significant differences between the two groups were observed for serum concentrations of individual immunoglobulins.
The possibility that DMSO might influence the antigenicity of SRBC was studied by pretreating red cells with 10% DMSO for 24 hr at room temperature. Washed, treated cells were used to immunize normal mice and the results were compared with a group of mice similarly injected with untreated red cells. No significant differences were noted between the two mouse groups for plaque-forming cells or hemagglutination titers.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
29.07.2003 (113)

Type : Immunotoxicity

Method : Autoimmune strain MRL/lpr, C3H/lpr, and male BXSB mice were placed on a continuous treatment regimen with 3% DMSO or 3% DMS02 in the drinking water, ad libitum, commencing at 1 to 2 months of age, before spontaneous autoimmune lymphoproliferative disease d evelopment could be detected. This represented doses of 8-10 g/kg/day of DMSO and 6-8 g/kg/day of DMS02.
Plasma antinuclear antibodies were analyzed employing an indirect immunofluorescence assay with chicken erythrocyte nuclei as substrate. Serum IgG was measured by radial immunodiffusion utilizing a quantitative immunodiffusion kit. Direct antibody plaque formation was measured using spleen cells from C3H/lpr mice that had been injected ip with 5 X 10e8 washed sheep erythrocytes (SRBC) 5 days previously.

Result : Both compounds were observed to extend the mean life span of MRL/lpr mice from 5.5 months to over 10 months of age. All strains showed decreased antinuclear antibody responses and significant diminution of lymphadenopathy, splenomegaly, and anemia development. Serum IgG levels and spleen IgM antibody plaque formation, however, did not differ from control values. There was no indication of involvement of systemic immunosuppressive or antiproliferative effects, and treated animais were observed to remain healthy and vigorous with no signs of toxicity. These results demonstrate that high doses of both DMSO and its major in vivo metabolite, DMSO2, provide significant protection against the development of murine autoimmune lymphoproliferative disease.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
12.09.2000 (110)

Type : Immunotoxicity

Method : Two groups of 8 female SW mice were injected i.p. daily with 2.5 g/kg 100% DMSO for one week, 1.3 g/kg every other day for the next week (because they appeared weak) and 2.5 g/kg daily for the following 3 weeks. Control mice received identical amounts of sterile saline by the same route. All mice were immunized sc with 0.05 ml 5% sheep red blood cells on days 13 and 24, and bled twice by caudal incision on days 20 and 29. Anti-SRBC hemagglutination titers were determined by doubling dilutions; leukocyte counts, hematocrits, and

organ weights (liver, lungs, spleen, thymus, kidneys, and heart) were measured by standard methods. The experiment ended after 36 days of treatment.

Result : In DMSO-treated mice, haematocrits were significantly decreased (p<=0.002) but still within the normal range. The primary and secondary antibody response to sheep red blood cells, leukocytes counts, body weight, and the size of the heart, lungs, spleen, thymus, and kidneys were not affected. DMSO treatment resulted in significant liver enlargement (p=0.02). It is concluded that DMSO is not deleterious to the humoral immune response in mice responding to a new antigen.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
12.09.2000 (28)

Type : other: initiation/promotion study

Remark : The effects of DMSO on the tumorigenic activity of dimethylbenz[a]anthracene (DMBA) was investigated in rats. Two groups of 50 male Sprague-Dawley rats were given 20 mg DMBA by gavage. DMSO (50 ppm the drinking water) was started 3 days before or 3 days after DMBA administration and administered for 18 months. A third group received no DMSO and served as untreated controls. DMSO had no beneficial or deleterious effect on the latency of the tumours induced by DMBA nor on the tumour frequency. Rats receiving DMSO weighed more and had fewer tumors than did the controls at the end of the 18-month study period. This was suggestive that DMSO decreased the total number of tumors, although the difference between treated and control rats did not reach statistical significance

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (61)

Type : other: initiation/promotion study

Remark : In 20 ICR/Ha Swiss mice, dermal application of 0.1 ml DMSO, 3 times weekly over a period of 400 days, after a primary treatment with DMBA (applied once only, 20µg in 0.1 ml acetone), induced no skin tumours.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (98)

Type : other: initiation/promotion study

Remark : The role of dimethyl sulfoxide ((DMSO) CAS: 67-68-5) in experimental tumorigenesis was investigated because of conflicting reports in the literature ranging from inhibition to no effect to enhancement. With the use of numbers of skin tumors produced on the back of the mouse following topical applications of carcinogenic agents as the variable and with acetone serving as the control solvent, the following results were obtained: When DMSO was the solvent for benzo(a)pyrene (CAS: 50-32-8) in the single-stage model (C3H mice), tumor numbers doubled. When DMSO was the solvent for 7,12-dimethylbenz(a)anthracene

(CAS: 57-97-6) serving as initiator in the two-stage model (CD-1 mice), tumor numbers were unaffected. In the two-stage model, when DMSO was the solvent for the potent promoter phorbol-12-myristate-13-acetate ((PMA) CAS: 16561-29-8) or was applied to skin at the initiation site (the back) before PMA, tumor numbers were reduced to one-third of control. However, when DMSO was applied before PMA to the abdomen, a site remote from initiation, tumor numbers doubled. Enhancement of PMA appears to be unique. Recognition that diverse effects can occur depending on the method of application of DMSO may help to decipher the conflicting literature on its relation to tumorigenesis, could be of value in probing the mechanism of tumor promotion, and might signal further caution in its clinical use.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (2) valid with restrictions
24.12.2002 (81)

Type : other: initiation/promotion study

Remark : The effect of intravesical instillation of dimethylsulfoxide (DMSO) on bladder carcinogenesis was examined in mice. Experiment 1: Fifty- five female C3H/He mice were administered 0.05% N-butyl-N-(4-hydroxy-butyl) nitrosamine (BBN) in their drinking water for 8 weeks. In week 9 they were divided into two groups consisting of 25 mice each. Then, under nembutal anesthesia the first group was given weekly intravesical inatillations of 0.1 ml DMSO (minimum 99.0%) for 10 weeks. The second group received no treatment except anesthesia. All mice were killed 30 weeks after the begining of the experiment and their urinary bladder resected for histological examination. The incidence of bladder carcinoma was 93.7% (15/16) and 27.7% (6/22) in groups 1 and 2, respectively. These incidences differed significantly between the two groups. Experiment 2: One hundred and twenty female C3H/He mice were divided into two groups. The first group was given 0.05% BBN in their drinking water for 5 weeks and then tap water. The second group was not given BBN. In week 6, the first group was divided again into three groups (1, 2 and 3) consisting of 28, 26, and 27 mice, respectively. The second group was divided into groups 4 and 5 consisting of 21 and 18 mice, respectively. Under nembutar anaesthesia groups 1 and 4 received weekly intravesical instillation of 0.05 ml DMSO (minimum 99.0%) from weeks 6 to 13, Group 2 received weekly intravesical instillation of 0.05 ml distilled water from weeks 6 to 13. Groups 3 and 5 received no treatment except anesthesia. 25% of the group 1 mice developed bladder carcinomas compared to 0% in the controls.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
29.07.2003 (115)

Type : other: General pharmacology

Remark : GENERAL PHARMACOLOGY
DMSO has stimulated speculation and imagination but few useful and incontrovertible data have been generated. DMSO's affinity for water, its superiority as a solvent, and its ability to trap oxygen related free radicals are firmly

established. DMSO's effectiveness as a penetrant, carrier, cryoprotectant, radioprotectant and as an antiischemic, antiinflammatory and analgesic agent are well established, but the mechanisms are incompletely understood. DMSO's systemic toxicity and teratogenicity are considered low. DMSO's local toxicity may be significant, depending on dose, route, species and individual variation. Combinations of DMSO with other agents may be dangerous. Potential complications should be considered, and investigated or avoided. Side effects of DMSO, such as mast cell degranulation, diuresis and volume depletion may exacerbate patient's preexisting problems, and should be considered before treatment is initiated.

1) Only veterinary preparations of DMSO should be used. The industrial solvents may contain impurities that can endanger health.
2) DMSO should be kept in an airtight bottle, and the bottle should be tightly closed when not in use. Exposed DMSO is rapidly diluted by water in the air, and becomes less effective.
3) DMSO should only be applied to a clean, dry, unmedicated skin surface. DMSO can carry unwanted substances through skin, into the body. DMSO's reaction with excess water on damp skin can produce more heat and discomfort than is necessary.
4) DMSO should be applied with sterile or clean cotton in order to minimize contamination with potentially dangerous substances and to minimize human exposure. Wearing rubber gloves will also help reduce human exposure to contaminants and to DMSO itself, but some compounds in solution with DMSO will even penetrate rubber gloves.
It is unfortunate when a potentially useful drug cannot be added to the approved medical arsenal because sufficient information is not available. Similarly, ineffective or dangerous drug applications should be exposed by well documented case reports and by well designed investigations. The medical professions, the patients and the drug deserve more thorough investigation of DMSO' s therapeutic potential, and its interactions with other drugs and disease states. Current evidence from in vitro situations and from laboratory animals suggests that DMSO may prove to be especially valuable in improving outcomes of intestinal surgeries , and in treatment of transient ischemic insults to organs or systems. Other areas that may be worthy of investigation by and for the veterinary profession include: post operative patient comfort and wound healing; ulcerative wound healing; acute swelling due to injury in other than equine species ; reduced metabolism and damage in ethylene glycol intoxication
because of alcohol dehydrogenase inhibition by DMSO; therapeutic combinations of DMSO with other drugs - antimicrobials, cytotoxic drugs in cancer chemotherapy, steroids; dangerous combinations of DMSO with other drugs ; dangerous interactions of DMSO with some disease states (e.g. mastocytoma).

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
29.07.2003 (20)

Remark : A. MEMBRANE PENETRATION - TRANSPORT
DMSO readily crosses most tissue membranes of lower animals and man. This property depends on a reversible configuration change of the protein occuring when DMSO subsitutes for water. DMSO in combination with electrolytes reduced the electrical resistance of the skin by facilitating the absorption of these electrolytes which it was itself being absorbed.
B. EFFECT ON COLLAGENE
After immersion in DMSO, the collagen fraction extractable with neutral salt solution was significantly decreased.
C. ANTIINFLAMMATION
Some antiinflammatory effects were demonstrated with intraarticular DMSO in rabbits following the creation of experimental (oil) arthritis.
D. ANALYSIS
DMSO produces analgesia by acting both locally and systemically, with a longer duration of action than morphine 6 hr vs 2 hr respectively.
E. BACTERIOSTASIS
Bacteriostasis from DMSO occures due to a loss of RNA conformational structure required for proteins synthesis.
F. DIURESIS
With the important increase in urine volume, there was an increase in Na and K excretion.
G. ENHANCEMENT
DMSO increase the effectiveness of Griseofulvin and potentiates the action of Digoxin.
H. CHOLINESTERASE INHIBITION
In vitro assays 0.8 - 8 % DMSO inhibits bovine erythrocyte cholinesterase 16 - 18 %.
I. VASODILATATION
DMSO possess potent histamine liberating properties.
J. MUSCLE RELAXATION
DMSO applied topically to the skin of patients produces electromyographic evidence of muscle relaxation after 1 hr.
K. ANTAGONISM TO PLATELET AGGREGATION
DMSO is a good antagonist in vitro and in vivo.
L. ENHANCEMENT OF CELL DIFFERENTIAITON AND FUNCTION
DMSO stimulates cyclic AMP accumulation and lipolysis and decreases insulin stimulated glucose oxydation in free white fat cells of rat.
M. RADIOPROTECTIVE AND CRYOPROTECTIVE ACTION
DMSO possess such properties widely used.
N. PROTECTION AGAINST ISCHEMIC INJURY
Studies have reported that DMSO can increase the synthesis of PGE1, a moderate vasodilator. It also inhibits the calcium-induced release of nor adrenaline in nerve terminals. These actions are likely to be involved in its ability to protect against ischemic injury.

Source : Atofina, Paris-la-Défense, France
Atofina Paris La Défense Cedex

Reliability : (4) not assignable
29.07.2003 (79)

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

Based on the available data for DMSO, no testing is proposed under the HPV Challenge Program.

The current members of the Association are: ATOFINA Chemicals, Inc., Gaylord Chemical Corporation and Toray Fine Chemicals Company, Ltd.

If you have questions, please contact me at (703) 669-5688 or via e-mail at ehunt@adelphia.net.

Sincerely,

Submitted electronically

Elizabeth K. Hunt
Executive Director

Cc: Richard Hefter, EPA
Leslie Scott, EPA