FOREWORD INTRODUCTION

N,N-DIMETHYLACETAMIDE (DMAC)

CAS N°:127-19-5

SIDS Initial Assessment Report for 13th SIAM

(Bern, Switzerland, 6-9 November 2001)

Chemical Name: N,N -Dimethylacetamide
CAS No: 127-19-5
Sponsor Country: Italy
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History:

This HPV chemical has been assigned to Italy in phase I of the OECD HPVC Programme.
It was discussed at SIAM 3 (1995), but according to the majority of delegates information was lacking. At the SIAM 11 (January 2001) a revised report was submitted too late for consideration, so that it was added to the agenda for the SIAM 12 (June 2001), but again comments couldn't be resolved at the meeting.

Testing:	No testing	(x)
	Testing	( )

Comments:

Deadline for circulation:
Date of Circulation:

Revised : September 2001

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	127-19-5
Chemical Name	N,N-Dimethylacetamide (DMAC)
Structural Formula	$CH_3CON(CH_3)_2$

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DMAC is well-absorbed orally, by inhalation and dermally. There are adequate data with which to evaluate the potential hazard to human health of this compound. DMAC has low toxicity by ingestion: the oral LD 50 ranges from 3000 mg/kg bw to 6000 mg/ Kg in rats and > 5000 mg/Kg bw in rabbits. The chemical is harmful by dermal route and inhalation: dermal LD 50 values were 7500 mg/kg bw in rats, 9600 mg/Kg bw in mice, from 2100 mg/kg bw to 3600 mg/Kg bw in rabbits, but less than 940 mg/ kg bw in guinea pig. Inhalation LC 50 rat was 8.81 mg/l, 1h (~ 2.2 mg/l, 4h) and LC 50 mouse was 1.47 mg/l, 3.5 h. DMAC is not a skin sensitiser or skin irritant and was only slightly irritating to the eyes. In repeated dose studies (14 days to 2 years) NOAECs of 25 ppm (0.09 mg/l) and higher have been observed in inhalation studies with rats and mice. Effects observed included liver degeneration, some irritation to the respiratory tract and decreased body weight gain. A NOAEL oral of 300 mg/Kg, 24 months, has been observed in oral studies with rats. Observation included kidney and adrenal weights. DMAC does not show mutagenic effects in several *in vitro* and *in vivo* tests. UDS in human diploide fibroblast and a transgenic mouse mutation assay on liver tissue are negative. For the *in vivo* tests two dominant lethal assays with rat (dermal and inhalation) were negative and dominant lethal assays on mouse (dermal, inhalation and i.p.) were negative too. A cytogenetic assay on human lymphocytes from 20 workers who were in contact with DMAC didn't reveal an increase in the frequency of chromosome aberration. DMAC was not carcinogenic in a two year drinking water study and a two year inhalation study in rats and to an 18 months inhalation study in mice. DMAC has been extensively studied for reproductive toxicity properties. Fertility was not affected when male rats had been exposed to up to 386 ppm (1.4 mg/l) in a 43 days inhalation study and in a 10 weeks one-generation inhalation study up to 300 ppm (1.08 mg/l) (females also were exposed). No effects in mice were observed in a sperm abnormalities test with exposures up to 700 ppm (2.52mg/l)for 6 weeks. Developmental toxicity was also investigated: the inhalation study in rats showed no adverse effects at the highest concentration, 300 ppm (1.08 mg/l), other than reduced maternal and fetal weight. The rabbit inhalation study showed a small increase in cardiac malformations at 570 ppm (2.052mg/L), in absence of maternal toxicity signs. The oral studies (rat and rabbit) indicate that high doses can cause both maternal and embryofetal toxicity. In an oral study on rat at 65, 160, 400 mg/kg bw/day the highest dose of DMAC was able to induce specific teratogenic effects such as great vessel malformations and anasarca at maternal toxic levels and the NOEL is 160 mg/kg bw/day. These findings were confirmed by a second oral study on rat performed at the same dose levels, from which a NOEL of 65-mg/kg bw/day can be derived. Due to the observed signs of specific developmental toxicity DMAC has to be considered a developmental toxicant.

Effects seen in the dermal studies (rat and rabbit) occurred at high and generally maternotoxic doses. A recent *in vitro* embryotoxicity study has been performed and embryotoxicity and teratogenic effects were observed at the highest levels. A NOEC was derived, corresponding to an *in vivo* NOEL of 100 ppm as the concentration in the plasma after the exposure to 100 ppm in air in another study, may be similar to the NOEL observed in this study. Liver impairment was observed in 19 out of 41 workers who had been working from 2 to 10 years in a spinning unit (airborne levels were not reported). Upper respiratory tract, gastric and nervous disturbances were complained. Biological monitoring of workers exposed to DMAC in an acrylic fibre plant was performed: brief threshold limit value-level exposures and chronic low level exposure do not cause hepatotoxic clinical chemistry responses. A retrospective epidemiologic study was undertaken in 571 workers with a 12-months simultaneous exposure to

acrylonitrile and no relationship between tumors and DMAC exposure was found. Also dermal absorption and inhalation of DMAC in human volunteers was carried out. They were exposed twice to DMAC for 4 h at intervals of 96 h or above to 6.1 ppm). Mean dermal absorption was estimated to be 40.4% of the total DMAC uptake. DMAC vapour was significantly absorbed through the skin. Biological half lives of urinary MMAC were 9h for skin and 5.6 h for lung respectively.

Environment

Releases of DMAC to the environment are to be expected with waste water (treated), solid wastes (incinerated), exhaust gas (in air by vent), and a residue in the raw acrylic fibres is < 0.5% by weight and in the raw elastane yarns from 0.1% to 3% by weight. DMAC has been tested in aquatic species: alga *Scenedesmus* 72 h -EC50 > 500 mg/l; daphnia 48 h - EC 50 > 500 mg/l, fish acute toxicity 96 h - LD 50 > 500 mg/l. A NOEC for *Daphnia* at 48 h is 1000 mg/l and for *Mysidopsis bahia* a NOEC at 96 h is 320 mg/l. Therefore DMAC is not acutely toxic to aquatic organisms. From the EC50 value for alga *Scenedesmus* of 500 mg/l a $PNEC_{aqua}$ of 0.5 mg/l can be derived by applying an assessment factor of 1000. This factor is justified as long term effect values are not available.

Exposure

The worldwide production volume of Dimethylacetamide in the year 2000 is estimated to be from 50000 to 60000 tons/ year. The substance is mainly used for polymer dissolution in the man-made fibre production industry. It is produced in closed system and processed at the production sites (non dispersive use). DMAC production is limited to the replacement of losses occurring during the production, processing and recovery. DMAC is also used in fine chemical industry. It is not intended to be used by the general public. DMAC is a colourless liquid, completely miscible with water, with a vapour pressure of 1.76 hPa at 20°C. It doesn't hydrolyse and undergoes photochemical degradation with half-life time of 6.1 hours. A bioconcentration factor (BCF) of 0.008, calculated from log octanol-water partition coefficient (log Kow) of –0.77, indicates a low bioaccumulation potential in aquatic species. A low adsorption to soils and sediments can be assumed by a calculated Koc of 9.1. DMAC is inherently biodegradable (77-83 % after 14 days). Distribution MacKay model indicates that considering a release of DMAC into the air, it is likely to be transported in water and soil.

Occupational exposure may occur through dermal contact and vapour inhalation during the use of DMAC. No exposure is envisaged during production and recovery of DMAC as this takes place in a closed system. An air extraction equipment placed above the processing units was adopted to limit any exposure and workers wear solvent-proof gloves during some critical operations, such as fibre spinning, so significant exposure is not expected.

Consumer exposure is negligible as results from migration tests with simulated sweating on textile articles containing residual DMAC (from 0.01% to 0.001%).

NATURE OF FURTHER WORK RECOMMENDED

No recommendation.

SIDS Initial Assessment Report

ACETAMIDE N.N-DIMETHYL

1. IDENTITY

OECD name:	Dimethylacetamide
Synonyms:	DMA, DMAC
CAS Number:	127-19-5
EINECS Number:	204-826-4
Empirical formula:	C4H9NO
Structural formula:	CH3-CO-N(CH3)2
Degree of Purity:	<99.7%
Major Impurities:	
Essential Additives:	None
Conversion factor	1 ppm= 3.6 mg/m^3

1.2 Physico-chemical properties

Appearance:	colourless liquid	
Melting point:	- 20	°C
Boiling point at 1013 hPa:	165	°C
Density:	0.9366	g/cm3
Water solubility:	Miscible in all proportions	
Vapour pressure at 20°C:	1.76	hPa
Vapour pressure at 40°C:	6.52	hPa
Log Pow:	-0.77	
Flash point (open cup)	70	°C
Flash point (closed cup)	63	°C
Auto Flammability.	490	°C
Explosive lower limit:	1.8	%(v/v)
Explosive upper limit:	11.5	%(v/v)

1.3 Classification

Official UE classification (as in Directive 67/548/EEC)

Harmful:	Xn	R 20/21-36
Concentration limits:	12.5%≤C<20%	Xn;R20/21
	C≥20%	Xn;R20/21-36

Proposal UE classification (as in the 28th Adaptation to Technical Progress close to publication in the O.J.)

Repr. Cat. 2:	T	R61
Harmful:	Xn	R20/21
Concentration limits:	C≥25%	T;R61-20/21
	5%≤C<25%	T;R61

MAK-Listing 1997 Substances classified for teratogenic risk
Category C (substance for which there is no reason to assume a risk to the unborn if the MAK value is not exceeded).

ACGIH-Listing 1999 Substances classified for carcinogenic risk
Category A4, SKIN (substance not classifiable as a human carcinogen)

"Use of the skin designation is intended to alert that air sampling alone is insufficient to accurately quantitate exposure and that measures to prevent significant cutaneous absorption may be required".

TLV-TWA (US): 36 mg/m3, skin
MAK (DE): 35 mg/m3
OEL (EU): 36 mg/m3, 8 hours, skin; STEL : 72 mg/m3, 15 min.

2. EXPOSURE

2.1 General discussion

Production levels:

Montefibre, BASF, Du Pont, Ertisa and Monsanto are the major producers of DMAC within the OECD countries. Others: AAKIM (Turkey) and U.C.B.(Belgium).The production sites are located in Italy, Germany, Belgium/Spain, and USA. The production volume in the year 2000 amounted to 3300 tons in Italy (Montefibre) and 7200 in Spain (Ertisa). The production capacity is 20000 tons/year in Germany (BASF). In the US (Monsanto and Du Pont) the chemical is estimated to be produced from 7700 to 13600 tonnes/Year and the worldwide production levels were estimated to be 50000-60000 tons/year.

Production

N,N-Dimethylacetamide is manufactured from acetic acid and dimethylamine in closed system.

Processing:

Most DMAC is principally used for polymer dissolution in man-made fibre production industry. The process uses the best recovery technology(>99% in Italy), so that DMAC production is only related to replace the solvent losses due to the acid hydrolysis during the recovery and to the environmental releases during the whole processing. Therefore the amounts of DMAC used at processing sites are significantly larger than the production levels.

Fibre production using DMAC in Europe amounted in 1997 to:

410'000 t/a of acrylic fibre using DMAC as the spinning solvent
25'000 t/a polyurethane elastane yarns, spun from DMAC
4'000 t/a meta-aramid fibres spun with DMAC as the solvent.

DMAC also may be used as a solvent for production of X-ray and photographic products (10-20%), reactor solvent for cosmetic and pharmaceutical intermediates (10-20%), aramid fibers (10-20%), polyimide films and polymers (<10%), resins and polymers (<10%), miscellaneous organic chemicals (<10%), and liquid treatment fibers (<10%); and solvent in production of photo-resist stripping compounds (<10%) (US EPA Use and Exposure Profile, 1995).
In Italy DMAC is sold to pharmaceutical and cosmetic industry as well as coating industry for industrial use only (about 30%) by virtue of its excellent solvent power for high molecular-weight polymers and synthetic resins and a good reaction medium and catalyst for a variety of organic syntheses.

Options for disposal:

In the case of disposal, DMAC can be incinerated or sent to a waste disposal treatment plant.

2.2 Environmental exposure and fate

The environmental releases during DMAC production and processing are divided in liquid losses, collected and degraded in the waste-water treatment, in gaseous losses, sent into the air by vent, in solid losses, sent to incinerator, and a residue onto the fibre.
DMAC manufacturing and processing releases from one of the three Italian plants (Porto Marghera) are approximately 1300 tons/year, with 30% released to air, 20% to waste water treatment plant, 8% to incinerator, and the remaining quantities as residue into the fibre (<0.5% by weight).DMAC manufacturing and processing releases as reported by Monsanto are approximately 4100 tons/year, with 40% released to air, 56% to land, and 4 % off site.
Emission data from other production and processing sites are not available.
Using the Mackay Fugacity Model the distribution of DMAC in the environment is calculated as:

	MacKay Level I model	Mackay Level III model
Air	0.54%	0.307%
Water	99.46 %	47.9%
Soil	0%	51.7%
Sediment	0%	0.095%
Biota	0%	-

The level III model calculation uses a release rate of 50 kg/hour (as it is for the Italian producer) and assumes that releases are to air only.
The results show that considering a release of DMAC into the air, it is likely to be transported in water and soil.
Biodegradability was studied in three tests. The first test corresponds to a Zahn Wellens test showing an ultimate degradation of 95% after 5 days. The second test is a MITI II test showing 77-83 % degradation after 14 days.
The third one is a MITI modified test (I) which shows a 70 % degradation after 28 days based on Oxygen consumption respect to ThOD (performed according to OECD guideline 301C)
DMAC results inherently biodegradable according to the first two tests. In the third test the ten days window shows a degradation near to 60% (57.5%), so that DMAC is a borderline case between a ready and an inherently biodegradable substance.
The ratio BOD5/COD is equal to 0.49 with acclimated river water as bacterial seed.
DMAC doesn't hydrolyse in aqueous solutions even at elevated temperatures. At a measured pH = 9.36 at 95 °C hydrolysis is less than 0.02% after 140 h.
If released to the atmosphere, DMAC may undergo a rapid gas-phase reaction with photochemically produced hydroxyl radicals. An estimated half-life for this process is 6.1 hours.
DMAC is not expected to bioaccumulate on the basis of a calculated BCF of 0.008 (from a log $K_{ow=}$ -0.77).
When released to the atmosphere, the chemical may photograde and may also undergo atmospheric removal by wet deposition processes which can result in a contamination of soil.

DMAC was detected in 6 of 6 air samples in 1982 within a mile radius of a hazardous liquid waste impoundment, location not given, at concentration from 9.6 ng/m^3 to 11 ng/m^3 (Guzewich et al. 1983).

Emissions in water are degraded at 60% in the waste-water treatment plant if considered as inherently biodegradable (about 87% according to Simpletreat model considering DMAC as ready biodegradable). If released to water, DMAC will not bioconcentrate in fish and aquatic organisms nor will it adsorb to sediment and suspended matter (soil adsorption coefficient = 9.1) or volatilise from water.

If released to soil, due to its high miscibility with water, DMAC will display very high mobility and will not volatilise from most soil.

2.3 Consumer exposure

Because the uses of DMAC are strictly industrial, consumer direct exposure to DMAC is not expected.

Textile articles containing acrylic are either 100% articles or in mixtures with, for example, wool or cotton, dyed or bleached. This reduces the DMAC content to <0.01% in relation to the acrylic. There is no risk involving escaping vapours or direct dermal contact as described below:
Migration tests with simulated sweating according to DIN 54020 show that, for instance, a person wearing socks made of 100% acrylic with a residual DMAC content $\leq$100 mg DMAC/kg acrylic or a person wearing a T- shirt made of the same synthetic material during extreme sweating lasting 10 hours would maximum uptake levels of 0.35 µg/kg body weight or 1.5 µg/kg body weight (body weight 60 kg). To estimate the risk from these textiles, one can use the OEL of 35 mg/m^3 DMAC, which takes into consideration the reprotoxicity potential (TLV- Threshold Limit Value – List, pregnancy group C) and the long exposure times at work, the air volume uptake of DMAC during a working shift could be assumed to be 10 m3, thus resulting in a basic value of 10 x 35 mg = 350 mg DMAC/day or approx. 5800 µg/kg body weight per day, at which level there is no risk.
A comparison with the above-mentioned potential DMAC uptake levels indicates safety factors of approx. 16'600 or approx. 3'800.
Taking into account the fact that acrylic is usually mixed with cotton or wool, the potential uptake of DMAC is reduced accordingly.

Textile articles may contain up to 30% elastanes. These textiles are subjected to a hot-wet treatment during production, e.g. dyeing or bleaching. This reduces the residual DMAC content to below 0.001%. For consumers, the residual amount does not represent a risk, as described below.
For example, a bathing suit weighting approx. 150 g. Assuming that residual DMAC is extracted by sweating and can penetrate into the body, sweat simulation tests lead to amounts of 10x0.15x0.1 mg DMAC or 2.5 µg/kg body weight taken up during a sweating period of three hours. In this case the safety factor is approx. 2300 (Bayer et al. 1998).

People living in the surroundings of DMAC processing plants may be exposed to low levels of the chemical. The total inhaled DMAC dose in a year is less than 10 min TWA.

2.4 Occupational exposure

TLV-TWA (ACGIH 1999) = 36 mg/m^3 = 10 ppm v/v Note: skin

OEL (OJEC 2000) = 36 mg/m^3 = 10 ppm v/v Note: skin
Short Term Exposure Limit Value (15 mins) = 72 mg/m^3 = 20 ppm v/v

No exposure in the DMAC production and recovery plant.

Occupational exposure to DMAC may occur by inhalation or dermal contact during its use.
Data from the National Occupational Exposure Survey (NOES) indicates that 8,000 to 43,000 workers are potentially exposed to DMAC at 9 to 2,000 facilities, but the concentrations to which they are exposed are not available.

Moderate releases occur due to the evaporation of the coagulation bath, during the acrylic fibres drying and annealing, and due to some spills in peculiar operations as change of filter clothes and starting of the spinning machine. Air extraction equipment above the units serve to limit exposure. Instructions for use of solvent-proof gloves prevent direct dermal contact with spinning solution and the solvent it contains. Direct dermal contact is only possible in case of misuse.
Inhalation exposure is limited by adhering to the established OEL and results below 18 mg/m^3 (Montefibre).

Based on monitoring data, submitted by Monsanto and DuPont on approximately 135 workers, DMAC manufacturing and processing personnel are estimated to have the following potential inhalation dose rates:

Monsanto

- Field operators: central tendency - 2.8mg/person/day; high-end-14.30mg/person/day;
- Pigment operators,: central tendency -3.24mg/person/day; high-end-64.19mg/person/day;
- Batch operators and sample operators: central tendency - 25.90mg/person/day; high-end-513.5 mg/person/day
- Senior operators, spinning operators, and utility operators and jet and dye room personnel : central tendency - 7.84mg/person/day; high-end - 44.41 mg/person/day;

DuPont

- Manufacturing personnel: potential inhalation dose rate - 1.40 mg/person/day;
- Tank car and tank wagon loading personnel: potential inhalation dose rate - 52.70 mg/person/day;
- Drum loading personnel: potential inhalation dose rate - 12.10 mg/person/day; and
- Maintenance personnel: potential inhalation dose rate - <4.45 mg/person/day.

Based on data, submitted by Monsanto and DuPont estimates of dermal exposure are as follows:

- Manufacturing and dope preparation personnel, spinning operators and utility operators, maintenance, drum loading, tank car and tank wagon loading personnel are assumed to have: two-hand contact with DMAC and a potential dermal dose rate between 1,300 to

3,900 mg/day;

- Senior operators and jet and dye room personnel are assumed to have incidental, one-hand contact and a potential dermal dose rate between 650 to 1,950 mg/day;

Preparation, drawing and drying of the tows take place in closed or semi-closed units fitted with air extraction equipment.
The remaining DMAC in the raw acrylic fibres delivered by the supplier is <0.5% by weight.
Inhalation exposure to DMAC due to escaping vapours is possible during secondary spinning. Confirmation at fibre customers (textile converters) has shown that exposure levels are below the OEL, e.g. in Ring Spinning or Open-End Spinning system <0.1 ppm, and in tow processing at the carding machines <5 ppm.
Dermal exposure from hand contact with acrylic fibres containing DMAC does not occur with dry skin. If the skin is sweaty, the maximum daily potential is approx. 10 µg/kg. Deriving a reference value of the OEL of 10 ppm, it becomes clear that no hazard is involved.

The same considerations are made for elastane yarns.
An estimation of direct dermal uptake during manual operations with spools on which elastane is wound containing residual amounts of DMAC (0.1-3% by weight) over a period of 8 days showed a maximum uptake of 1.5 µg on sweaty hands or 0.025 µg/kg body weight. This amount is extremely small taking into account the reference basis of approx. 5800 µg/kg and represents no health risk (Bayer et al. 1998).

Also the EASE estimation was carried out and the resulting predicted vapour exposure to DMAC ranges from 1.0 ppm to 3 ppm (3.6- 10.9 mg/kg bw).

3 HAZARDS TO THE ENVIRONMENT

3.1 Ecotoxicity

Acute toxicity data to fish for DMAC was investigated on seven different species and summarised in Table 2. There were no data available on chronic toxicity tests.

Table 2: Toxicity of DMAC to fish

Species	Parameter	Concentration mg/l	Reference
Oryzias latipes	Median Tolerance Limit 24h and 48h	1000	Tonogai et al., 1982
Leuciscus idus	NOEC	500	BASF, 1979
Gambusia affinis	LC_{50} – 96h	13300	Kennedy, 1986
Pimephales promelas	LC_{50} – 96h 23.1 °C	>/=1500	Geiger et al., 1990

Toxicity to daphnia

Acute toxicity data for DMAC to daphnia are summarised in table 3. There were no data on long term/reproduction tests.

Table 3: Toxicity of DMAC to daphnids

Organism	Endpoint	Concentration mg/l	Reference
Daphnia Magna	EC0 24 h	=500	BASF, 1988
Daphnia Magna	EC0 48h	= 500	BASF, 1988
Daphnia Magna	NOEC 48h	>/=1000	Adema, 1987

Acute toxicity data of DMAC to other organisms are summarised in table 4.

Table 4: Toxicity of DMAC to other organisms

AQUATIC ORGANISMS			
Algae			
Scenedesmus subspicatus	EC50 (72 h)	> 500 mg/l	BASF, 1988
Crustaceans			
Mysidopsis bahia	96h-LC_{50} NOEC	966 mg/l 320 mg/l	Adema, 1987
Chaetogammarus marinus	NOEC	>=1000 mg/l	Adema, 1987
TERRESTRIAL ORGANISMS			
Eisenia foetida	LC50	0.01 – 0.1 mg/cm^2 filter paper	Roberts, 1983
MICROORGANISMS			
Escherichia Coli	MIC	= 0.425 mg/l	TOXALL 1987
Pseudomonas putida	LOEC	4850mg/l (biomass growth)	BASF, 1986

Most tests are limit tests and a NOEC was not established except for *Mysidopsis bahia*.
A static test with *Daphnia magna* was performed with 10 animals in 250 ml of test solution at 20°C at the nominal concentrations of 0, 1.0, 3.2, 10, 32, 100, 320, 1000 mg/l, with an exposure time of 48 hours. The pH and oxygen concentration were monitored during the test period for all test solutions. No mortality was found during the exposure period, so that NOEC is higher than 1000 mg/l.
A semistatic test with daily renewal of the test medium and an exposure time of 96 hours was conducted with two marine crustaceans: *Chetogammarus marinus* and *Mysidopsis bahia*. (Adema 1987)
One test animal per container, 10 animals per test concentration at the nominal concentrations of 0, 320, 1000 mg/l for *C. marinus* and 0,320, 560, 1000, 1800 mg/l for *M. Bahia* for 96 hours. No mortality was found during the exposure period for *C. marinus*, so that NOEC is higher than 1000 mg/l. A NOEC of 320 mg/l was established for *Mysidopsis bahia*.
From all these data DMAC doesn't result acutely toxic to aquatic organisms.
Since no long term data on aquatic organisms are available, the value of EC50 for algae, 72 hours, of 500 mg/l, was chosen to calculate PNEC. The resulting PNEC is 0.5 mg/l using 1000 as assessment factor.
The test with *Eisenia foetida* doesn't follow strictly the OECD guideline N° 207. Soil was not used, so that it is not possible to convert the result which is expressed as mg/cm^2 of filter paper in mg/ kg of soil. The study was carried out with 90 chemicals and the relative toxicities of chemicals to earthworms were assessed. DMAC resulted very toxic to earthworm according to a toxicity ranking system were organophosphorus insecticide resulted extremely toxic and carbamate insecticides resulted supertoxic. The test with *E.Coli* is suggested to be used only as a primary screening test for toxicity because there was a very little correlation between MIC (Minimal Inhibitory Concentration = 0.425 mg/l) and LD50.

4 HUMAN HEALTH HAZARD

4.1 Toxicokinetics and metabolism and mechanism of action

Metabolism

33 mg or 92 mg of ^{14}C-labelled DMAC were given by gavage to two rats. The major urinary components were:60-70% MMAC, 7-10% N-hydroxymethylacetamide, 7-10%, Acetamide and some residual DMAC. A small proportion of DMAC and its intermediates was hydrolysed and eliminated as Carbon Dioxide.

Twenty male rats were given two subcutaneous injections of 300 mg DMAC, MMAC and Acetamide were found in the urine.

20 rats had 20-80% DMAC solutions (0.12 ml) applied to their backs. The amount of MMAC increased as the solution concentration increased. Recovery ranged from 13% for the 20% solution to 42% for undiluted DMAC (Du Pont, 1988).

These studies show that the major metabolic pathway of DMAC "in vivo" in rats is sequential N-demethylation and elimination from the body.

Distribution and excretion

3 male rats were exposed to 5 ppm of ^{14}C -DMAC for 12 hours. DMAC was found in the urine (41% of total recovered ^{14}C), then in the faeces and expired air (14% and 15% of total ^{14}C, respectively). At the end of post-exposure period, the carcass and tissues contained about 22% of the total ^{14}C. Fat and muscles were major sites of retention (Du Pont, 1988).

Male rats and male mice were exposed (Whole body) to 50, 150, 300 and 500 ppm DMAC with single exposures (1h,3h,6h) or repeated exposures (6h for ten times) DMAC plasma half-life in rats ranged from 0,6 to 1,5 h. MMAC persisted in plasma for at least 24h after the 150, 300 and 500 ppm exposure. Regardless of exposure level, repeated DMAC exposures resulted in plasma profiles of DMAC and NMAC similar to those from a single exposure. (Hundley et al., 1994)

There are some human data on excretion of DMAC in which urine samples from 5 workers were examined for 4 consecutive weeks. Airborne DMAC appeared to account for the greatest amount of urinary MMAC detected at the exposure concentrations encountered (0.5 to 2 ppm). A relationship of 10 ppm urinary MMAC for each 1 ppm DMAC inhaled was observed (Kennedy and Pruett, 1989).

A recent study with twelve healthy male volunteers was conducted. They were exposed twice to DMAC for 4 h at intervals of 96 h or above to 6.1 ppm for dermal (whole body with respiratory mask) and for inhalation exposure (nose only). Mean dermal absorption was estimated to be 40.4% of the total DMAC uptake. Biological half-lives of urinary MMAC were 9 h and 5.6 h via skin and lung respectively. DMAC vapour was significantly absorbed through the skin (Nomiyama, 2000).

4.2 Acute toxicity

Acute oral toxicity

Oral LD50 for DMAC is in the range from 3000 mg/kg bw to 6000 mg/kg bw in rats. This range includes nine values and is considered as very low acute oral toxicity. Deaths occurred after 24 hours from ingestion. Most organs were hemorrhagic, nerve cells degenerated, andliver and kidney necrosis were observed at autopsy. LD50 was > 5000 mg/kg bw in rabbits by gavage. DMAC was administered by gavage to dogs at 235,470,940 and 1880 mg/kg bw and the highest dose was lethal for all animals (Du Pont, 1988).

Acute dermal toxicity

Dermal LD 50 for rats was 7500 mg/kg bw (Stula and Krauss, 1977). For mice it was 9600 mg/kg bw on three groups of two mice dosed at 1000, 2500, 5000 and 10000 mg/kg bw: no deaths at 1000 or 2500 mg/kg bw, one of the two mice died at 5000mg/kg bw and both at 10000mg/kg bw (Wiles and Narcisse 1971).

Dermal LD 50 was 2100-3600 mg/kg bw in rabbits. Lethal doses produced degeneration of the brain, hearth, liver and kidneys while no mortality or irritation were observed at 500 mg/kg bw or less. Guinea pig LD50 dermal was less than 940 mg/kg bw (Du Pont, 1988).

Acute inhalation toxicity

Some acute inhalation toxicity animal studies have been reported.

The lowest LC50 rat was 8.81 mg/l, 1 hour exposure, which can be assumed to correspond to about 2.2 mg/l for a four hours exposure. (Watts, 1978).

The range in various rat studies is from 8.81 to 10.1 mg/l with 1 hour exposure and it is 1.47 with 7 hours exposition with liver parenchymal degeneration signs.

Six rats were also exposed to 12 mg/l at 20 °C and 50 °C to DMAC vapours for eight hours and observed for two weeks. No deaths were recorded (Smyth 1962).

The lowest LC50 for mice was 1.47mg/l for 3.5 hours. In this study ten mice were exposed to 406 ppm (1.47 mg/l) for 3.5 hours and ten mice were exposed to 575 ppm (2.08 mg/l) for 7 hours (Du Pont, 1988).

Two mice showed at autopsy marked degeneration of the liver and considerable degeneration of renal tubules. Lungs were congested and hemorrhagic in one animal.

The intraperitoneal LD 50 value was 2000 mg/ kg for rats, 2250 mg/kg for mice.

The intravenous LD 50 was 1860 mg/kg for rats and 2320 mg/kg for mice (Du Pont, 1988).

Eye irritation

DMAC caused mild and reversible irritation to eyes when applied undiluted at 0.1 ml. (Du Pont, 1984).

In a range finding study on rabbits on 500 compounds DMAC resulted as grade 3 in a scale where grade 1 indicates at most a very small area of necrosis resulting from 0.5 undiluted chemical in the eye and grade 5 indicates severe burns from 0.005 ml. and grade 10 indicates severe burn from 0.5ml of a 1% solution in water or propylene glycol (Smyth et al., 1962).

Nevertheless two rabbits receiving three drops of a 50% solution showed severe (but not scored) erythema, lacrimation and edema (Du Pont, 1988).

Also the UE classification considered DMAC not to be irritant because of mild and reversible effects.

Skin irritation
DMAC is not irritant to skin when applied undiluted to rabbits in 100, 250, 500 mg/dose group to the clipped skin. Irritation was observed during acute dermal toxicity studies on guinea pigs with contact times of 24 hours at rather high doses (Wiles and Narcisse, 1971).

Skin sensitisation
DMAC is not sensitising on guinea pig.

4.3 Repeated dose toxicity

Oral repeated toxicity
The longest repeated oral study is reported in Du Pont (1988). Male and female rats were dosed with 100, 300, 1000 mg/Kg in drinking water for 24 months (nominal concentrations). Slight alopecia and moderately severe hemosiderosis of the spleen were observed at the highest dose level. Decreased body weight gain was observed at all dose levels. Liver weights were increased in all groups and kidney weights were increased at 1000 mg / kg at six months interval and at 300 mg/kg at the end of the study. Also adrenal weights were increased at six months interval at all dose levels. A NOEL cannot be derived.
A NOAEL= 300 mg/kg bw day can be assumed for oral toxicity.
This value was chosen being the lowest one from oral studies and because this study was the longest one.

Inhalation repeated toxicity
In the inhalatory study of Malley et al. (1995) male and female rats and mice were exposed to 25, 100, 350 ppm for 6 hours/day, 5days/week, for 2 years.
Lower body weight gain only in rats at 350 ppm. Serum sorbitol dehydrogenase activity was increased in rats at 350 ppm. Serum cholesterol and glucose levels significantly higher at 100 and 350 ppm in female rats.
Rats exposed to 100 and 350 ppm showed liver weight increase hepatic focal cystic degeneration, hepatic peliosis, biliary hyperplasia (350 ppm only).
Mice exposed to 100 and 350 ppm (at 350 ppm females mouse only) had increased liver weight. Rats and mice at 100 and 350 ppm showed lypofucsin/hemosiderin accumulation in Kupfer cells and centrilobular single cells necrosis (mice only).
Male rats exposed to 350 ppm had also higher kidney weight correlated with a chronic progressive nephropathy.
Female mice exposed to 350 ppm had an increase incidence of bilateral diffuse retinal atrophy.
No effects were observed at the lowest exposure level with rats and mice, so that a NOEL = 25 ppm (corresponding to 6.41 mg/kg bw/day for male rat) has been assumed for inhalation toxicity.
This value was chosen being the lowest one from inhalation studies.

In the repeated inhalatory study on rat of Horn (1961) exposure to 40 ppm (145 mg/m^3) for 6h/day for 6d/week, 6 months, DMAC produced only marginal histopathological evidence of lung irritation, while at 100 ppm (362 mg/m3) there was significant dose-dependent toxicity, with nasal and upper respiratory tract irritation (Horn 1961).

Dermal repeated toxicity
Dermal studies on rabbits were conducted, but they didn't give NOELs, while a NOEL of 95 mg/kg bw/day results from a dermal study with dogs treated with 95; 299; 945; 3780 mg/kg for 5h/day, 5 days/week for 6 weeks .
Some effects (degeneration of liver and some skin irritation) were seen at 945 mg/kg, while only one dog lost weight early in the treatment at 299 mg/kg, but recovered (Horn 1961).

4.4 Reproductive toxicity

Fertility

Two inhalation studies on rats:
In the one generation reproduction study of Ferenz and Kennedy (1986) groups of 10 male and 20 female and females rats exposed to 0,30,100,300 ppm(31, 101 and 291 ppm actual concentrations) didn't show clinical evidence of toxicity and effects on body weight gain. Treatment was conducted for 6 h/day for 10 weeks before breeding, then 7 days week through breeding, gestation, lactation, with an interruption for females from gestation day 21 to postnatal day 4. Pups were examined on postnatal day 21. No adverse effects on mating, fertility, gestation, parturition, litter size and number of postnatal survival of the pups: the only effect observed was a reduced pup weight of 7% and increased relative liver weight in the top dose group (300 ppm) at 21st day post partum. No adverse effect on postmortem examination of the pups. Increased relative liver weight in the parenteral males at 100 and 300 ppm and in females at 300 ppm. Inhalation at 300 ppm is known to be toxic to the liver and respiratory tract but did not have any effect on fertility and pregnancy or embryofetal development other than a small effect on pup postnatal weight at weaning (Ferenz and Kennedy, 1986). In the study of Wang (1989) four groups (n=12) of male rats were exposed to 0,40,116 and 386 ppm DMAC 99.8% and mated to untreated females. They were treated for 6h/day, 5 day/w for a total of 43 exposure days prior the initiation of mating and 69 total exposure days up to sacrifice. No adverse effects on fertility, litter size or number, resorptions, fetal weight or malformation visible externally. No signs of toxicity in males other than increase of absolute and relative liver weight at 120 and 400 ppm. No adverse effects on testes weight or histopathology. (Wang G.M. et al. 1989)In a sperm abnormality test male mice were exposed to 20 and 700 ppm for 7hours/day for 5 days/w for 6 weeks. They were not mated and sperm was analysed 5 weeks after the end of exposure. No differences in frequency of sperm abnormalities between exposed groups and controls (Fairhurst et al., 1992).

Developmental toxicity

DMAC has been tested for developmental toxicity in many studies by oral, dermal and inhalation exposure routes. DMAC is well absorbed by the three routes and the relevant exposure routes in occupational setting are inhalation and dermal.

Groups of pregnant rats were exposed 0,30,100,300 ppm (0, 0.11, 0.36, 3.11 mg/l) (measured concentrations 0, 32, 100 or 282 ppm) DMAC by inhalation for 6 hours/day from 6 to 15th day of gestation.

Dams exposed at 300 ppm had reduced bodyweight gain during the treatment period (especially day 6-9). Fetal weights were slightly reduced. No embryofetal mortality or teratogenicity was observed. A modest dose-related increase in post implantation losses (litter mean: 1.0+/- 0.2 vs 0.6+/- 0.2 in controls) was the only detectable sign at this exposure level. No maternal or fetal effects were seen at 100 ppm

Maternal	NOEL	100 ppm (0.36 mg/l)
Teratogenicity	NOEL	100 ppm

(Solomon et al., 1991)

Groups of pregnant rats were dosed dermally with 600, 1200, 2400 and 4800 mg/kg bw on days 9,10 and 11; 11 and 12; or 12 and 13 of gestation.
No maternal or foetal toxicity at 600 mg/kg bw. Signs of maternotoxicity, increase of resorption rate and three malformed fetuses at 1200 mg/kg bw. Encephalocele was found at 2400 mg/kg bw in 3/34 fetuses. This study is not appropriate because of a low number of animals and it is scarcely reported.
The same study on rabbits similarly treated with 200 mg/kg bw didn't show any embryotoxic effect and malformations.

Teratogenicity	NOEL	200 mg/kg bw

(Stula, 1973)

Another dermal study on rabbits at 125,250,500 mg/kg bw from 6 to 18th day of gestation didn't show toxicity effects in dams and/or effects on number of resorptions or live foetuses. At the top dose one foetus had skeletal abnormality (deviation of sternum).

Maternal	NOEL	500 mg/kg bw/day
Teratogenicity	NOEL	250 mg/kg bw/day

(Monsanto, 1973)

Groups of pregnant rabbits were exposed 0,2; 0,7; 2 mg/l (57, 200, 570 ppm) DMAC by inhalation for 6 hours/day from 7 to 19th day of gestation until 29 th day of gestation.
No treatment related effect on dams were observed.
A significantly increase in reduced ossification and a not statistically significant increase in heart and great vessel malformation at the top dose level.

Maternal	NOEL	2 mg/l
Teratogenicity	NOEL	0.7 mg/l

(BASF, 1989)

DMAC in aqueous solution was administered orally to 4 groups of pregnant rabbits at 0,94,282,470 mg/kg bw from 6 to 18th day of gestation. At the highest dose group the treatment induced mortality in the dams (2/ 11) and 100% in the conceptuses: four cases of cleft palate in 3/10 litters and one fused ribs and microphthalmia at 282 mg/kg bw, no malformations at 94 mg/kg bw.. At 282 mg/Kg bw and at 94 mg/Kg/ bw there was reduced food intake and bodyweight gain in the dams.

Teratogenicity	NOEL	94 mg/kg bw/day

(Merkle and Zeller, 1980)

Groups of 22-25 pregnant rats were dosed with 0, 65, 160, 400 mg/kg bw by gavage- 14 days from 6 to 19 th day of gestation. No treatment related toxic signs were observed in the dams though animals in all groups including controls had evidence of viral infection which may have compromised the study. There was a reduction in mean maternal body weight gain throughout the treatment period and gestation at the 400 mg/Kg /day level statistically significant ($p<=0.05$). In the 160 mg/Kg/day group, a slight reduction in body weight gain was apparent in the 0-to 20-day interval adjusted weight. Mean maternal body weights throughout the treatment period at the 65 mg/kg/day level were comparable to the control group.

At the highest dose level there was a very small but significant increase in resorption (2.6 vs 1.2 per dam), but no reduction in number of live implants. The most important finding was a large number of foetuses with malformations mostly at the level of cardiovascular system (33 foetuses from 18 litters affected, which were reported to be very unusual in the animals used). There was also some retardation of ossification which is compatible with the reduced foetal weight. So a clear teratogenic potential at 400 mg/kg bw which is also toxic to the dams. It is unlikely that malformations are secondary to maternal toxicity because of high incidence and specificity of such defects to the cardiovascular system. The dose response for teratogenicity is very steep since no malformations were observed at the next lower dose of 160 mg/kg bw.

Maternal	NOEL	65 mg/kg bw/day
Teratogenicity	NOEL	160 mg/kg bw/day

(Johannsen et al., 1987)

A more recent study confirmed the findings of the Johannsen study exposing groups of 24-25 pregnant rats by gavage to 20,65,150,400 mg/kg bw DMAC from 7 to 21th day of gestation with examination of the fetuses on day 22.

At 400 mg/kg bw there were marked maternal toxicity (reduced body weight gain, weight loss, reduced food intake). Increase in absolute and relative kidney weight and relative liver weight, but no histopathological evidence of organ damage and no changes in clinical chemistry. Mean maternal weight change was reduced during the dosing period for animals dosed at 150 and 400 mg/Kg. There were no dose-related effects on maternal weight changes at either 65 or 20 mg/Kg.

Embryolethality was evidenced by increase in resorption (3.1 per litter vs 0.5 in controls) and reduced litter size (10.4 vs 14.1) and reduced fetal weight. Large number of malformed fetuses in the top dose level at gross necroscopy (69/250 from 17 litters, viscerally (133/206, 24 litters) or skeletally (13/250- 7 litters). The majority of malformations were of the head (synotia, naris atresia, micrognatia, cerebral ventricle distension), cardiovascular system (heart and great vessels defects, pulmonary artery) and a variety of skeletal defects at low incidence.

Minimal developmental toxicity at 150 mg/kg bw : slight reduction in maternal body weight gain and in fetal body weight. No other effect except one fetus with multiple malformations including naris atresia, heart and great vessels malformatons and micrognatia.

No embryotoxic effects at lower dose levels

Maternal	NOEL	65 mg/kg bw/day
Teratogenicity	NOEL	65 mg/kg bw/day

(Du Pont, 1997)

Recently in vitro embryotoxicity was investigated and the results of this study show embryotoxicity and teratogenic effect only at the highest dose levels (3.5 and 5 mM), with a no-effect concentration of 0.85 mM. The authors point out that the results of this work agree with those obtained by Solomon et al (1991) in their experiment by inhalation, in which the no-effect level for embriotoxicity was 100 ppm, as the plasma concentration after exposure to 100 ppm in air may be similar to the no-effect concentration observed in this study.
So that 0.85 mM can be considered corresponding to the NOEL of 100 ppm (corresponding to a dose level of about 54 /kg bw/day) obtained in the Solomon study of 1991. The authors suggest that it may be a matter of discussion whether the TLV value (10 ppm corresponding to 5.4 mg/kg bw/day) is enough for an adeguate protection of female workers (Menegola et al., 1999).

4.5 Genetic toxicity

Genetic toxicity were tested through several bacterial tests, three non bacterial in vitro tests and seven mammalian in vivo tests.

Bacterial tests
Tests were done using *Salmonella typhimurium* strains TA 1535,TA 1537, 1538, TA 100,TA 98 at different concentrations ranging from 0.05 mg/plate to 15 mg/plate both with and without metabolic activation. No increase in mutation frequencies in any of the strains. Just in one test result was ambiguous. Another test was performed using E.Coli WP2 and WP2uvrA up to 4000 mg/plate with and without exogenous metabolic activation system and it resulted negative.

No bacterial test in vitro
DMAC increased the frequency of sister chromatid exchange in CHO cells at 10,15,20,25 ul/ml and was toxic at the top dose, but results were ambiguous.
The unscheduled DNA synthesis assay was conducted with human embryonic intestinal cells, rat liver S9 and 70 to 9366 µg/ml DMAC: there was no indication of any increase in the number of silver grains per nucleus at any concentration of DMAC, while the positive controls induced significant responses in UDS in these cells.
DMC was non mutagenic in a transgenic mouse mutation assay on liver tissue were it was used as control substance while studying the mutagenicity of adolezesin.

Genetic toxicity in vivo

A cytogenetic analysis of rat bone marrow cells was performed after in vivo exposure to 20 or 700 ppm DMAC for 7 h/day for 5 days: there were no indications of induction of chromosomal damage in either the exposed male or female rats. (Mc Gregor, 1981).
Also a cytogenetic assay on human lymphocytes from 20 workers who were in contact with DMAC didn't reveal an increase in the frequency of chromosome aberration, but controls were lacking (Du Pont, 1988).
In the dominant lethal assay performed by Mc Gregor (1981) male rats (10/group) were exposed by inhalation 7hours/ day on five consecutive days at DMAC concentrations of 20ppm or 200ppm. Each male was mated to two untreated females a week for 9 weeks. The females were sacrificed ten days after the mating week and examined for pregnancy and dominant lethal effects (early resorption sites). Results indicate no increase in

resorption in females mated to the treated males. Normal mating indices and pregnancy rates were seen. This treatment regimen did not produce an increase in dominant letals.
Other dominant lethal assays were conducted dermally with rats and mice at 1500 and 3000 mg/kg bw; by inhalation at 0.72 and 2.53 mg/l and i.p (680 ul/kg aqueous solution) with mouse. All test results indicate that DMAC is considered a low concern for genetic toxicity.

The sex linked recessive lethal test was performed using *D. melanogaster* after 95 minute exposure to 200 ppm. At one hour from the beginning of exposure there were decreased activity and at the end of exposure activity of the flies was greatly reduced. A frequency of lethals of 0.57 % was detected. This was due to three lethals derived all from a single male, so that this high frequency was not interpreted as indicative of mutagenic response (Mc Gregor, 1981).

4.6 Carcinogenicity

Rats were given 100, 300, 1000 mg/kg bw by drinking water for two years. There are no lesions related to treatment in rats killed at 12 months and in male rats killed at 24 months or dying during the time between the two scheduled sacrifices. In female rats killed at 24 months or dying after 12 months, the incidence of thymomas was slightly higher in animals given DMAC then in controls. The incidence was 0/50 in the control group, 1/50 (2%) in the 100 mg/kg group, 0/50 in the 300 mg/kg group and 3/50 (6%) in the high-dose group. These tumours, which occur spontaneously in Long-Evans rats with a somewhat variable incidence, showed no dose-response relationship and are not thought to be related to treatment (Monsanto, 1980).
Rats and mice were exposed by inhalation to concentration of 25, 100, 350 ppm for 6 hours/day and 5 days/week, respectively in a two year and in a 18 months study. The incidence of hepatic tumors and testicular tumors were similar to control for all exposure concentrations in males and females and there aren't compound-related effects on the incidence of other tumours in either sex at any exposure concentration.
There was only a statistically significant increase in squamous cell papilloma in the stomach at 350 ppm for females rats and in lymphoma at 350 ppm for female mice, both within the range of hystorical controls and not compound related.
These studies are already described as chronic toxicity studies in the repeated dose toxicity section (Malley et al., 1995).
Hamsters were treated dermally for 6 weeks, 3 days/week. Doses were not reported and DMAC lowered the yelds and incidents of total tumors, and particularly advanced tumors promoted by retinyl acetate or croton oil after initiation by 7,12-dimethylbenz(a)-anthracene.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

a) Environment

On the basis of tests showing some effect DMAC is of low toxicity to aquatic organisms. The most sensitive species is the green algae *Scenedesmus suspicatus*. From the EC50 value of 500 mg/l a $PNEC_{aqua}$ of 0.5 mg/l can be derived by applying an assessment factor of 1000. This factor is justified as long term effect values are not available.
DMAC doesn't hydrolyse in aqueous solutions, even at elevated temperature; it is inherently biodegradable and the industrial waste water are treated biologically in a sewage treatment plant.

Data of Log Pow and BCF indicate a low bioaccumulation potential in aquatic species. DMAC shows low toxicity to fish, daphnia and bacteria. It shows high toxicity to earthworms, but due to its high mobility and biodegradability it is not expected to accumulate in soil nor to reach dangerous concentrations.
The Danish EPA QSAR Estimation system predicts a generally ready biodegradability and low to moderate aquatic toxicity.
The environmental and consumer exposures are negligible and the exposure in the workplace is lower than the TLV.

b) Human Health

DMAC is classified harmful by inhalation and skin contact according the criteria of Directive 67/548 EEC.DMAC has been comprehensively studied in animals. DMAC is well-adsorbed orally, by inhalation and dermally and shows moderate acute toxicity by all routes of exposure. It is a slight skin irritant and a mild to moderate eye irritant. It shows some chronic toxicity effect to the liver and irritation to respiratory tract. Minimal signs of irritation on histopathological examination of the lungs of rats exposed to 40 ppm DMAC. At 100 ppm and above there was significant dose related toxicity with the upper respiratory tract and liver. It would thus appear that the target organs showing toxicity at the lowest exposure levels are the liver and the respiratory tract.
Human evidence from case reports demonstrates there is a clear relationship between liver impairment and DMAC exposure duration in men occupationally exposed (airborn levels not reported)(Corsi, 1971).
In other studies chronic low level exposure (<5ppm) doesn't cause hepathotoxic clinical chemistry response (Spies et al., 1995).

DMAC has no effect on fertility.
Oral and inhalatory studies on rabbits do not show clear teratogenic effects related do DMAC. They indicate that high doses of DMAC can cause both maternal and embryofetal toxicity.
The rat inhalation study showed no adverse effects at the highest concentration (300 ppm) other than reduced maternal and fetal weight.
In an oral study on rat DMAC was able to induce specific teratogenic effects (heart great vessels malformations) even if at maternotoxic levels.

The rabbit inhalation study showed a small increase in cardiac malformations at 570 ppm. This finding is of some concern given the high incidence of cardiac malformations seen in the oral rat study.
These findings were confirmed by a second more relevant study (Du Pont Haskell, 1997).
Effects seen in the dermal studies on rats and rabbits occurred at high and generally maternally toxic doses.
Due to the high dosages required to cause the developmental effects (400 mg/kg bw) DMAC has been considered a low potency developmental toxicant by the European Specialised expert Working Group which fixed to 5 % the specific classification limit of concentration to be taken into account for preparations containing DMAC.
DMAC is a developmental toxicant at high exposure levels respect to the exposure patterns.

DMAC is clearly not mutagenic in a battery of tests including Ames test, dominant lethal in rats or mice, UDS in vitro assay, cytogenetic analysis in bone marrow, in Drosophila SLRL test, and in sperm abnormality test in mice.

DMAC was not carcinogenic in a two-year drinking water study in rats and in a 18-month inhalation study in rats and mice. Also in a epidemiological cohort study it is concluded there is no relationship between DMAC exposure and mortality from tumours. 571 workers simultaneously exposed to acrylonitrile for at least for 12 months (Mastrangelo et al., 1993).

5.2 Recommendations

Considering, the toxicological and ecotoxicological data and the overall limited exposure for man and environment because this compound is produced for industrial use only, it can be concluded that the chemical is not a candidate for further work.

6. References

Adema D.M.M. and G.H. van den Bos Bakker (1987) Aquatic toxicity of compounds that may be carried by ships (Marpol 1973, Annex II). A progress report for 1986. Report n. R 86/326a. TNO Netherlands:1-20.

Applegate V.C. et al. (1957). Special Sci. Report Fishes, No. 207.

Bayer, Du Pont, Ertisa, Fisipe, Montefibre, CIRFS (31/08/98) Not published.

BASF AG (1977), Ecological Laboratory-Unpublished Data.

BASF AG (1979) Unpublished report 78/277.

Cors G.C. (1971). Med. Law., 62, 28:1-15.

Du Pont Haskell Labs (1997) (HL-1997-00203). DMAC: Developmental toxicity study in Sprague-Dawley rats.Unpublished data.

Du Pont (1984) Haskell Laboratory . Toxicity studies on DMF and DMAC with cover sheets and letter dated 092484. EPA/OTS:Doc. 86-8900007478.

Du Pont (1988)- Haskell Laboratory Internal DMAC Review, Oct. 1988 Unpublished Data.

Fairhurst S et al. HSE Criteria document for an OEL N,N-Dimethylacetamide published by HMSO C20, London 1992.

Ferenz R.L. and G.L. Kennedy (1986). Fundam. Appl.Toxicol., 7:132-137.

Geiger D.L. et al. (Eds.) (1990). Acute toxicities of organic chemical to fathead minnows (pimephales-promelas). Vol. V. Superior WI:133.

Guzewich DC et al.; Air sampling around a Hazardous Liquid Surface Impoundment. 76th Ann Mtg Air Pollut Contr Assoc paper 24.1 (1983).

Horn H.J. (1961). Toxicol. App. Pharmacol., 3:12-24.

Hundley S.G. et al. (1994) Toxicology Letters 73, 213-225.

Johannsen F.R. et al. (1987). Fundam. App. Toxicol. 9:550-556.

Kennedy G.L. and J.W. Pruett (1989). J. Occ. Med., 31(1):47-50.

Kennedy G.L. (1986) CRC Crit. Rev. Toxicol.,17:129-182 from Wallen I.E. et al. (1957). Sewage Ind. Wastes, 29:695.

Malley L.A. et al. (1995) Foundamental and Applied Toxicology 28, 80-93.

Mc Gregor D.F.(1981),Tier II Mutagenic screening of 13 NIOSH priority compounds:DMAC Rep N° 33 1981 PB83-13390-0.

Menegola E. et al. (1999) , Toxicology in Vitro, 13: 409-415.

Merkle J. And Zeller H. (1980). Arzneim. Forsch./Drug Research, 30, 9:1557-1562.

Mostrangelo et al. (1993). J. Occup. Med., 43 (3) 155-8

Nomiyama T. et al. (2000). Int. Arch.Occup. Environ. Health, vol. 73, n°2, 121-126.

Report to Montefibre from Biffi (1995). DMAC: Biodegradation by modified MITI test. Biolab Report n. 94/20164:1-8.

Roberts B.L. and H.W. Dorough (1984) Environ. Toxicol. Chem. 3(1):67-78.

SIDS Dossier on the HPV Phase I Chemical : N,N-Dimethylacetamide (revised August 2001).

Smyth H.F. et al.(1962). Am. Ind. Hyg. Assoc. J., 23:95-107.

Spies G. J., et al (1995). J. Occup Envir. Med. 1102-1107

Stula E.F. et al.(1973). Du Pont - Haskell Laboratory - Unpublished Data: Pathology Report No. 60-73.

Stula E.F. and Krauss, W.C. (1977), Toxicol. Appl. Pharmacol., 41:35.

Tonogai Y., Ogawa S., Ito Y. and M. Iwaida (1982). J. Toxicol. Sci., 7:193-203.

TOXALL- Data Bank from Kennedy G.L. (1986). Drug Chem Toxicol., 92(2):147-170.

US EPA (1995) Use and Exposure Profile for Dimethylacetamide.

Wang G.M. et al. (1989). J. Toxicol. Environ. Health, 27:297-305.

Watts J.C. (1978) Du Pont Company Data, Haskell Laboratory, Unpublished Data: Report no 69-79-MR no 3025-002.

Wiles J.S. and J.K. Narcisse (1971). Am. Ind. Hyg. Assoc. J., 32:539-545.

I U C L I D D a t a S e t

Existing Chemical	ID: 127-19-5
CAS No.	127-19-5
EINECS Name	N,N-dimethylacetamide
EC No.	204-826-4
TSCA Name	Acetamide, N,N-dimethyl-
Molecular Formula	C4H9NO

Producer Related Part	
Company:	OECD
Creation date:	12-SEP-2003
Substance Related Part	
Company:	OECD
Creation date:	12-SEP-2003
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 13 (6-8 November 2001)

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1.0.1 Applicant and Company Information

Type: sponsor country
Name: Istituto Superiore di Sanità

Country: Italy
24-MAR-2004

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

Smiles Code: CH3CON(CH3)2
Mol. Formula: C4H9NO
Mol. Weight: 87.1

12-SEP-2003

1.1.1 General Substance Information

Substance type: organic
Physical status: liquid
Purity: > 99.7 - % w/w

22-OCT-2003 (127)

1.1.2 Spectra

1.2 Synonyms and Tradenames

ACETIC ACID DIMETHYLAMIDE

12-SEP-2003

ACETYLDIMETHYLAMINE

12-SEP-2003

DIMETHYLACETAMIDE

12-SEP-2003

DIMETHYLACETONE AMIDE

12-SEP-2003

DIMETHYLAMIDE ACETATE

12-SEP-2003

DMA

12-SEP-2003

DMAC

12-SEP-2003

1.3 Impurities

Contents: <= .3 - % w/w

04-NOV-2003

1.4 Additives

CAS-No: 127-19-5
EC-No: 204-826-4
EINECS-Name: N,N-dimethylacetamide
Contents: % w/w

Remark: Not Added
22-OCT-2003

1.5 Total Quantity

Quantity: = 50000 - 60000 tonnes produced

Remark: Montefibre, Basf , Du Pont, Ertisa and Monsanto are the major producers of DMAC within the OECD countries. Others:AAKIM (Turkey) and U.C.B.(Belgium) The production sites are located in Italy, Germany, Belgium/Spain, and USA. The production volume in the year 2000 amounted to 3300 tons in Italy(Montefibre) and 7200 in Spain. Germany (BASF) production capacity is 20000 tons/year. In the US the chemical is estimated to be produced from 7700 to 13000 tonnes/Year and the worldwide production levels were estimated to be 50000-60000 tons/year. Montefibre is the only Italian Dimethylacetamide producer.
24-MAR-2004 (56)

1.6.1 Labelling

Labelling: as in Directive 67/548/EEC
Symbols: (Xn) harmful
Specific limits: no
R-Phrases: (20/21) Harmful by inhalation and in contact with skin
(36) Irritating to eyes
S-Phrases: (26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(28) After contact with skin, wash immediately with plenty of
(36) Wear suitable protective clothing

Remark: Note: SKIN
24-MAR-2004

Labelling: other, as in legislation: ACGIH (1999). Threshold limit values and biological exposure indices. Cincinnati, Ohio, 25 (supplement n.1 - January 2000).
Specific limits: no

Remark: Note: A4, SKIN
24-MAR-2004

1.6.2 Classification

Classified: as in Directive 67/548/EEC
Class of danger: other: toxic for reproduction, category 2; harmful
R-Phrases: (61) May cause harm to the unborn child
(20/21) Harmful by inhalation and in contact with skin
Specific limits: yes
Conc./Class. 1: 5% =< T R61
C <
25%
Conc./Class. 2: C >= T R61-20/21
25%

Remark: Repro Cat 2: T R61
Harmful: Xn R20/21
28th Adaptation to technical progress
24-MAR-2004

1.6.3 Packaging

1.7 Use Pattern

Type: industrial
Category: Textile processing industry

Remark: Solvent
12-SEP-2003

Type: type
Category: Non dispersive use

04-NOV-2003

Type: use
Category: Solvents

Remark: Solvent for polyacrylonitrile.
12-SEP-2003 (46)

Type: use
Category: Solvents

Remark: spinning solvent for textile fibers (10-20%) DuPont 1993
12-SEP-2003 (135)

Type: industrial
Category: other: fine chemical industry

Remark: solvent for production of X-ray and photographic products (10-20%), reactor solvent for cosmetic and pharmaceutical intermediates (10-20%), aramid fibers (10-20%), polyimide films and polymers (<10%), resins and polymers (<10%), miscellaneous organic chemicals (<10%), and liquid treatment fibers (<10%); and solvent in production of photo-resist

stripping compounds (<10%) - DuPont
12-SEP-2003 (135)

Type: industrial
Category: other: fine chemical industry

Remark: In Italy DMAC is sold to pharmaceutical and cosmetic industry as well as coating industry (about 30%) by virtue of its excellent solvent power for high molecular weight polymers and synthetic resins and a good reaction medium and catalyst for a variety of organic syntheses.
04-NOV-2003

Type: use
Category: Solvents

Remark: The next bibliography is reported in HSDB-Data Bank:

-Solvent for plastics, resins, gums and electrolytes; chemical reaction medium and catalyst; paint remover; high-purity solvent for crystallization and purification (Hawley G.G. (1977). The condensed chemical dictionary. 9th Ed., Van Nostrand Reinhold Co., New York:303).

-Solvent tested as drug vehicle and as antitumor agent (Gosselin R.E., H.C. Hodge, R.P. Smith and M.N. Gleason (1976). Clinical toxicology of commercial products - Part II 4th Ed., Williams and Wilkins, Baltimore:135).

-Solvent for stabilization of prostglandins in solution (Israeli Patent Number 44740,06/15/78 (UpJohn Co.)).

DMAC is used as a chemical intermediate (Du Pont (1988). DIMETHYLACETAMMIDE: Properties, Uses, Storage and Handling. (Printed in U.S.A.:11).

Solvents used in pharmaceutical formulations (Kim S.N. (1988). Drug Metab. Rev., 19:345-368).
24-MAR-2004 (22) (32) (35) (40) (45)

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

12-SEP-2003

1.8.1 Occupational Exposure Limit Values

Type of limit: other: TLV-TWA (US)
Limit value: 36 mg/m3

Remark: TLV-TWA (US)
The TLV value points out the danger of absorption through the skin too.
23-OCT-2003 (1) (13)

Type of limit: MAK (DE)
Limit value: 35 mg/m3

12-SEP-2003 (5)

Type of limit: other: OEL (EU) (8 hours)
Limit value: 36 mg/m3
Short term exposure
Limit value: 72 mg/m3
Schedule: 15 minute(s)

Remark: Note SKIN
12-SEP-2003 (59)

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: ITALY

Production is performed in closed system.
It is used in the same factory or others, as a solvent.
Most DMAC is used for polymer dissolution in textile processing industry, it's utilized in fine chemical industry, too.

The process in the three textile industry (MONTEFIBRE) is showed in annex 1 (flow sheet).
The DMAC, coming from the recovery and production plants, is feeded in a feeder extruder together the polymer. The solution (25% weight polymer) is extruded in a bath through some spinnerets at 90°C. The polymer coagulates as a yarn.
Solvent and water (used to coagulate and wash the fiber) are sent to recovery plant.
Moderate releases occur due to the evaporation of the coagule bath, during the fiber drying and annealing, and due to some spills in peculiar operations as change of filter clothes and starting of the spinning machine. Air extraction equipment above the units serve to limit exposure.
Instructions for use of solvent-proof gloves prevent direct dermal contact with spinning solution and the solvent it contains.
Direct dermal contact is only possible in case of misuse.
Inhalative exposure is limited by adhering to the established OEL.

The DMAC values in workplace (italian plants) are below TLV

limits (18 mg/m3 TWA).

DMAC production is only related to replace the solvent losses due to the environmental releases and the acid hydrolysis during the recovery (>99% in Italy). The environmental releases are divided in liquid losses, collected and completely degraded in the waste-water treatment, in gaseous losses, sent into the air by vent, in solid losses, sent to incinerator, and a residue onto the fibre. DMAC manufacturing and processing releases from one of the three Italian plants (Porto Marghera) are approximately 1300 tons/year, with 30% released to air, 20% to waste water treatment plant, 8% to incinerator, and the remaining quantities as residue into the fibre (<0.5% by weight).
See Annex to SIDS Dossier

04-NOV-2003

Remark: EUROPE
The remaining DMAC in the raw acrylic fibers delivered by the supplier is < 0.5% by weight.
Inhalative exposure to DMAC due to escaping vapours is possible during secondary spinning, The air is monitored to stay below the OEL of 10 ppm of DMAC.
Confirmation at fibre customers (textile converters) has shown that exposure levels are below the OEL, e.g. in Ring Spinning or Open-End Spinning system < 0.1 ppm, and in tow processing at the carding machines < 5 ppm.

12-SEP-2003 (16)

Remark: USA

DMAC manufacturing and processing releases as reported by Monsanto are approximately 4100 tons/year, with 40% released to air, 56% to land, and 4 % off site

Estimated Occupational Inhalation and Dermal Exposures Associated

with the Manufacture and Processing of DMAC (Monsanto Company, Decatur, AL)

Type of Worker		Number of Workers/Hours Per Day/Days Per Year[1]	Range of Airborne Concentrations (mg/m^3)[2]		Potential Inhalation Dose Rates[3] (mg/person/day)		Potential Dermal Dose Rate[4] (mg/day)
			Central Tendency[5]	High-end[6]	Central Tendency	High-End	
Manufacturing Personnel	Field Operators	8/0.25 - 1/>250	1.06	2.49	2.8	14.30	1,300 - 3,900
Dope Preparation	Pigment Operators	4/0.25 - 1/>250	9.30	51.35	3.24	64.19	1,300 - 3,900
	Batch Operators Sample Operators	8/1 - 8/>250	9.30	51.35	25.90	513.5	1,300 - 3,900
Spinning Personnel	Senior Operators	16/0.25 - 1/>250	7.02	35.53	7.84	44.41	650 - 1,950
	Spinning Operators	48/0.25 - 1/>250	7.02	35.53	7.84	44.41	1,300 - 3,900
	Utility Operators	8/1 - 8/>250	7.02	35.53	62.7	355.3	1,300 - 3,900
	Jet Room Personnel Dye Room Personnel	8/1 - 8/>250	7.02	35.53	62.7	355.3	650 - 1,950

[1]Information needed to determine the exposure for individual worker activities was not available.
[2]mg/m^3 = ppm x MW/24.45; where MW = molecular weight of 87.12 g/mole and 24.45 L/mole is molar volume.
[3]Based on medium work inhalation rate of 1.25 m^3/hr and an 8 hour/day.
[4]Assumes no dermal protection and the chemical is 100% concentrated (CEB, 1991).
[5]Central tendency value is the arithmetic mean of the 1992, 1993, 1994 concentrations for each type of worker on Exhibit 2-16.
[6]High-end value is the maximum value of the 1992, 1993, 1994 concentrations for each type of worker on Exhibit 2-16.

Estimated Occupational Inhalation and Dermal Exposures Associated with the Manufacture and Processing of DMAC (DuPont Specialty Chemicals, Belle, WV)

Type of Worker	Number of Workers/Hours Per Day/Days Per Year[1]	Range of Airborne Concentrations[2] (mg/m^3)		Potential Inhalation Dose Rates[3] (mg/person/day)		Potential Dermal Dose Rate[4] (mg/day)
		Central Tendency	High-end	Central Tendency	High-End	
Manufacturing Personnel	15/1-8/100-250	0.14		1.40		1,300-3,900
Tank car and Tank Wagon Loading Personnel	5/1-8/100-250	5.27		52.70		1,300-3,900
Drum Loading Personnel	5/1-8/100-250	1.21		12.10		1,300-3,900
Maintenance Personnel	10/0.25-1/100-250	<3.50		<4.45		1,300-3,900

[1]Information needed to determine the exposure for individual worker activities was not available.
[2]mg/m^3 = ppm x MW/24.45; where MW = molecular weight of 87.12 g/mole and 24.45 L/mole is molar volume.
[3]Based on medium work inhalation rate of 1.25 m^3/hr and an 8 hour/day.
[4]Assumes no dermal protection and the chemical is 100% concentrated (CEB, 1991).

04-NOV-2003 (135)

1.11 Additional Remarks

Memo: OPTIONS FOR DISPOSAL

Remark: 1. By absorbing it in vermiculite, dry sand, earth or a similar material and disposing in sealed containers in secured sanitary landfill.
2. By atomizing in a suitable combustion chamber equipped with an appropriate effluent gas cleaning device.

- DMAC can be incinered in a authorized incinerator for chemicals.
- Can be used after re-conditioning.
- Can be incinerated, when in compliance with local regulations. Contact waste disposal services.
- Can be biodegraded, by a specialized contractor, when in compliance with local regulations.
- Wastes with concentration of DMAC greater than 25% are considered harmful.

04-NOV-2003 (25) (28) (48)

Memo: INFORMATION ON TRANSPORT

Remark: Road and rail transport:
RID/ADR: Class / ORD.LE / No. KEMLER /
CT/FS: Category N.C. No. ONU /

Sea transport:
IMDG Code: ONU n. N.C. Class. Pag.
DPR N0. 1008/1968 and foll. mod. Class. Letters

Air transport:
ICAO/IATA: ONU No. Class
DMAC when dissolved in water caused rust in steel tanks
12-SEP-2003 (3) (27)

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Value: = -20 degree C
Decomposition: no at degree C
Sublimation: no

Year: 1979

22-OCT-2003 (138)

2.2 Boiling Point

Value: = 165 degree C at 1013 hPa
Decomposition: no

Year: 1979

22-OCT-2003 (138)

2.3 Density

Type: density
Value: = .9366 g/cm³ at 25 degree C

Year: 1979

22-OCT-2003 (138)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = 1.76 hPa at 20 degree C

Method: other (measured)
Year: 1990
GLP: no data

Remark: Antoine constants:
In P=A-B/(C+T) where
P in hPa; T in degree C
A = 9.9925
B = 2750.5
C = 209.62
The mean deviation of the values is 0.32%
22-OCT-2003 (5) (10)

Value: = 6.52 hPa at 40 degree C

Method: other (measured)
Year: 1990
GLP: no data

22-OCT-2003 (5)

2.5 Partition Coefficient

log Pow: = -.77

Method: other (calculated)
Year: 1988

22-OCT-2003 (83)

log Pow: = -.796 at 25 degree C

Method: other (measured): OECD Guide-Line 1979
Year: 1982
GLP: no data

Test condition: DMAC was dissolved in distilled water or in n-octanol at the concentration of 100 mg/l.
22-OCT-2003 (134)

2.6.1 Solubility in different media

pH value: = 4
Conc.: 200 g/l at 20 degree C
Descr.: miscible

Method: other
Year: 1986
GLP: no data

Remark: Miscible with water in all proportions
22-OCT-2003

pH value: = 4.7
Conc.: 200 g/l at 25 degree C

Method: other
Year: 1988
GLP: no data

22-OCT-2003 (17)

2.6.2 Surface Tension

2.7 Flash Point

Value: = 70 degree C
Type: open cup

Method: other
Year: 1990
GLP: no data

Test condition: The value is in accordance with DIN 51 758
22-OCT-2003 (5) (118)

Value: = 63 degree C
Type: closed cup

Method: other
Year: 1988
GLP: no data

22-OCT-2003 (17)

2.8 Auto Flammability

Value: = 490 degree C

Year: 1978

22-OCT-2003 (118)

Value: = 400 degree C

Method: other
Year: 1990
GLP: no data

Test condition: The value was tested in accordance with DIN 51 794.
This value is indicated as Ignition Temperature.
22-OCT-2003 (5)

2.9 Flammability

Result: flammable

Remark: Flammability = 2
Materials which must moderately heated before ignition will occur. Water spray may be used to estinguish fire because material can be cooled below its flash point.
04-NOV-2003 (118)

Result: flammable

Remark: Combustible Liquid Class IIIA
04-NOV-2003 (93)

Result: flammable

Remark: EXPLOSIVE LIMITS:
1.8% (lower) - 11.5% (upper) by vol. in air
04-NOV-2003 (60)

Result: flammable

Remark: 1.7 (lower) -- 11.5 (upper) Vol percent
02-DEC-2003 (5)

2.10 Explosive Properties

Result: not explosive

22-OCT-2003 (127)

2.11 Oxidizing Properties

Result: no oxidizing properties

Remark: REACTIVITY = 0
Materials which (in themselves) are normally stable even under fire exposure conditions and which are not reactive with water.
22-OCT-2003 (118)

2.12 Dissociation Constant

2.13 Viscosity

2.14 Additional Remarks

Memo: Additional Remarks

Remark: Violent reaction with halogenated compounds when heated above 90°C. Iron powder catalyzes the reaction so that it initiates at 71°C. When heated to decomposition it emits toxic fumes of NOx.
04-NOV-2003 (128)

Remark: In presence of iron salts exothermic reaction with halogenated hydrocarbons at elevated temperatures.
04-NOV-2003 (5)

Remark: Extreme caution must be exercited if strong oxiding agents are to be mixed with DMAC.
04-NOV-2003 (21)

Remark: DMAC is stable to its atmospheric boiling point in the absence of acidic and alkaline materials. It distills essentially unchanged with no colour or acid formation. Above 350°C degradation to ammoniacal products and acetic acid occurs (thermal decomposition).
04-NOV-2003 (20)

Remark: At normal pressures and in the absence of water, alcohols, strong acids or bases, DMAC is resistant to light and air, even when it is heated to boiling point. The rate of hydrolysis is minimal at room temperature and it is largely unchanged at elevated temperatures.
04-NOV-2003 (10)

Remark: VAPOR DENSITY (air=1) = 3.01
04-NOV-2003 (128)

Remark: SATURATED CONCENTRATION in AIR at 20°C = 12 g/m3
04-NOV-2003 (10)

Remark: EVAPORATION RATE = 172 (respect to diethyl ether)
DIN 53 170
04-NOV-2003 (10)

Remark: HENRY'S LAW CONSTANT = 1.22*10-8 atm*m3/mole a 25°C
04-NOV-2003 (119)

Remark: SURFACE TENSION = 34 DYNES/CM at 20°C
04-NOV-2003 (120)

3.1.1 Photodegradation

Type: air
epsilon (295): 0
Conc. of subst.: 936.6 g/l at 25 degree C
INDIRECT PHOTOLYSIS
Sensitizer: OH
Conc. of sens.: 500000 molecule/cm³
Rate constant: = .000000000062984 cm³/(molecule * sec)
Degradation: = 50 % after .3 day(s)

Method: other (calculated)
Year: 1995
Test substance: as prescribed by 1.1 - 1.4

Remark: DMAC doesn't absorb in visible range but only in the ultra-violet one.
ESTIMATED INDIRECT PHOTODEGRADABILITY

SUMMARY: HYDROXYL RADICALS

Hydrogen Abstraction = 2.894 E-12 cm3/molecule-sec
Reaction with N, S and -OH = 60.000 E-12 cm3/molecule-sec
Addition to Triple Bonds = no
Addition to Olefinic Bonds = no
Addition to Aromatic Rings = no
Addition to Fused Rings = no

OVERALL.OH Rate Constant = 62.9894 E-12 cm3/molecule-sec

HALF-LIFE = .255 Days (at conc. 5E5.OH/cm3)
=6.1 hours

SUMMARY: OZONE REACTION
No Ozone reaction estimation (only Olefins and Acetylenes are estimated).
Test condition: The DMAC concentration indicates the PURE SUBSTANCE.
24-MAR-2004 (80) (131)

3.1.2 Stability in Water

Type: abiotic
Degradation: <= 0 % after 140 hour(s)
at pH 9.4 and 95 degree C

Method: other
Year: 1960
GLP: no data

Test substance: DMAC containing 5% water by weight (20.2 mole percent
21-NOV-2003 (57)

Remark: DMAC shows only a slight tendency to hydrolyze in aqueous increases in the presence of acids or alkalis.
For hydrolysis in the presence of small concentration of acid or base see the Table. The END PRODUCTS are ACETIC ACID or ITS SALT, and DIMETHYLAMINE or ACID SALT.
DMAC also can undergo alcoholysis in the presence of acids to the corresponding ester, and dimethylamine.

TABLE: Hydrolysis of DMAC in acidic and basic solutions

Acid or Base	Initial Water content (wt %)	Temp. (°C)	Time (hr)	Hydrolysis (%)
H2SO4 0.096 N	5.07	30	264	0.48
		50	289	0.49
		95	25	0.36
(CH3)4NOH 0.02 N	7.48	30	264	0.35
		50	288	0.31
		95	264	0.39

04-NOV-2003 (18)

Remark: As DMAC is stable to hydrolysis except under strongly acidic or basic conditions, it is not expected to hydrolyze under typical pHs found in the environment.
04-NOV-2003 (115)

3.1.3 Stability in Soil

Remark: No Available Data
23-OCT-2003

3.2.1 Monitoring Data (Environment)

Medium: air

Remark: DMAC was detected in 6 of 6 air samples in 1982 within a mile radius of a hazardous liquid waste impoundment, location not given, at concentration from 9.6 ng/m3 to 11 ng/m3.
22-OCT-2003 (33)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: volatility
Media: water - air
Method: other: calculated

Result: An experimental Henry's Law constant of 1.22E-8 atm*m3/mole at 25°C indicates that DMAC will not volatilize from either water or moist soil to the atmosphere.
Based on this value, the estimated half-life for volatilization of the chemical from a model river (1 m deep, flowing at 1 m/sec with a wind speed of 3 m/sec) is 2800 days.
22-OCT-2003 (117)

Type: adsorption
Media: water - soil
Method: other: calculated

Remark: A soil adsorption coefficient of 9,1 (Lyman et al., 1982), also calculated from its experimental log octanol/water

partition using an appropriate regression equation, indicates that N,N-dimethylacetamide will not adsorb to sediment and suspended organic matter.
22-OCT-2003 (117)

Type: volatility
Media: soil - air

Remark: An experimental Henry's law constant of 1.22*10-8 atm*m3/mole at 25°C indicates that DMAC will not volatilize from moist soil to atmosphere. Based on its vapour pressure, 2.0 mm Hg at 25øC, DMAC volatilization from dry soil to the atmosphere will be slow.
22-OCT-2003 (121)

Type: desorption
Media: other: soil - water
Method: other: calculated

Remark: If released to soil, a soil adsorption coefficient of 9,1 (Lyman et al.,1982), calculated from its experimental log octanol/water partition coefficient of 0.77 indicates that DMAC will display very high mobility.
22-OCT-2003 (117)

Type: adsorption
Media: other: air - water, soil
Method: other: calculated

Remark: The miscibility of DMAC in water indicated that it may undergo atmospheric removal by wet deposition processes.
22-OCT-2003 (115)

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (calculation)
Year: 1990

Result: Mackay level I
Distribution of DMAC in different environmental comparts (expressed as % of added DMAC):

air	0.54
water	99.46
soil	0.
fish	< 0.001
sediment	0.
suspended sediment	0.

The logPow value used for computation was -0.77.
04-NOV-2003

Media: air - biota - sediment(s) - soil - water
Method: other (calculation)

Remark: Estimation was based upon release data (Italy) contained in section 1.9 of the dossier. Hourly air emission rate used in the input value is 50kg/hour.
Result: Mackay level III
Distribution of DMAC in different envioronmental

compartments (expressed as % of DMAC):

air	0.307
water	47.9
soil	51.7
sediment	0.095

04-NOV-2003

3.4 Mode of Degradation in Actual Use

Remark: Waste coming from the process of DMAC production and from recovery plant (see annex 1) are sent to industrial sewage treatment plant where they are treated biologically.

04-NOV-2003

3.5 Biodegradation

Type: aerobic
Inoculum: activated sludge, industrial
Concentration: 400 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: = 96 % after 5 day(s)
Result: inherently biodegradable

Method: other
Year: 1977
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Test condition: The method used could not clearly be identified as a "Zahn-Wellens test". It was performed in a closed system, the endpoint was "Total Organic Carbon" (the measurement method is not clear though) and the ratio inoculum (dry weight)/test substance was < 1. Furthermore the inoculum was activated sludge from an industrial waste water treatment plant. No elimination after 3h or 1d were recorded. Nevertheless, the results are in line with those from the MITI II test, so that the substance can be classified as inherently biodegradable.

24-MAR-2004 (84)

Inoculum: activated sludge
Concentration: 30 mg/l related to Test substance
Degradation: ca. 77 - 83 % after 14 day(s)
Result: inherently biodegradable

Year: 1992
Test substance: as prescribed by 1.1 - 1.4

Test condition: The test was performed additioning 30 mg/l of DMAC on 100 mg/l of sludge

22-OCT-2003 (14)

Type: aerobic
Inoculum: other: activated sludge, industrial & domestic, non adapted
Concentration: 100 mg/l related to Test substance
Degradation: = 70 % after 28 day(s)
Result: readily biodegradable
Kinetic: 1 day(s) = 8.7 %
2 day(s) = 23.7 %

```
                      7 day(s)    = 54 %
                     11 day(s)    = 55.3 %
                     12 day(s)    = 57.5 %
Kinetic:             14 day(s)    = 58.2 %
                     21 day(s)    = 63.8 %

Method:           other: Directive 92/69/EEC, part 7, pag. 216 (MITI I)
  Year:           1995
   GLP:           yes
Test substance:   as prescribed by 1.1 - 1.4

Remark:           The ten days window  shows a degradation  near to 60%, so
                  that DMAC is a borderline case between a ready and an
                  inherently biodegradable substance.
22-OCT-2003                                                          (66)


3.6 BOD5, COD or BOD5/COD Ratio

B O D 5

  Method:
    Year:         1988
     GLP:         no data
  Concentration:  1 g/l related to Test substance
  BOD5:           ca. 900 mg/l

C O D

    Year:
     GLP:         no data
COD:              = 1840 mg/g substance

R A T I O   B O D 5 / C O D

  BOD5/COD:       ca. .49
Method:
Remark:           Data on the 20-day BOD are unvailable but the value is
                  expected to approach the COD of the compound.
                  The calculated incremental oxygen demand for complete
                  nitrification (BOD-N) is 0.73 grams of oxygen per gram of
                  DMAC. The nitrogenous oxygen demand would be exerted at a
                  slower rate than the carbonaceous BOD.
                  Experience indicates that the effective biological
                  wastewater treatment may be achieved if bacteria are
                  acclimated to DMAC. Unacclimated bacteria will provide only
                  partial oxidation of the compound.
Test condition:   The test used pure DMAC and acclimated river water as
                  bacterial seed.
22-OCT-2003                                                          (19)


3.7 Bioaccumulation

Exposure period:  at 20 degree C
BCF:              = .01

Method:           other: (calculated
  Year:           1990
Test substance:   as prescribed by 1.1 - 1.4
```

Remark: Because the logPow is very low, the chemical is believed to be not bioaccumulable.
Test condition: The Bcf value calculated from mathematical model and the used log Pow value was -0.77.
24-MAR-2004 (31)

3.8 Additional Remarks

Remark: No additional remarks
23-OCT-2003

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 1000 -

Method: other: Japan Industrial Standards, 1971
Year: 1982
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Test condition: The test was performed at 25°C and the LC50 was determined after 24 and 48 hours.
Also after 24 h the LC50 was 1000 mg/l.
22-OCT-2003 (134)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: = 500 -
LC50: > 500 -
LC100: > 500 -

Method: other: DIN 38412 part 15 (Draft)
Year: 1979
GLP: no

Test substance: DMAC at purity at 99.5%
22-OCT-2003 (8)

Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
NOEC: >= 5 -

Method: other
Year: 1957

Test condition: Aerated fresh water at 13 degree C.
Test substance: DMAC purity not available.
04-NOV-2003 (90)

Species: Petromyzon marinus
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
NOEC: >= 5 -

Method: other
Year: 1957

Test condition: Aerated fresh water at 13 degree C on larvae of the sea lamprey.
Test substance: DMAC purity not available
04-NOV-2003 (90)

Species: Salmo gairdneri (Fish, estuary, fresh water)

Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
NOEC: >= 5 -

Method: other
Year: 1957

Test condition: Fresh sea water at 13 degree C, with aeration through standard stone airbreakers at near oxygen saturation
Test substance: DMAC purity not available.
04-NOV-2003 (90)

Species: Gambusia affinis (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 13300 -

Year: 1957
Test substance: no data

23-OCT-2003 (73)

Type: flow through
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: >= 1500 -

Year: 1990
GLP: no data
Test substance: no data

Test condition: Temperature 23.1 °C , dissolved oxygen 6.6 mg/l, hardness 45 mg/l CaCO3, alkalinity 43.5 mg/l CaCO3, pH 7.7.
23-OCT-2003 (116)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: = 500 -
EC50: > 500 -
EC100: > 500 -

Method: other
Year: 1988
GLP: no
Test substance: no data

Test condition: Method: Acute Toxicity for Daphnia, EEC Directive 79/831, March 1989.
23-OCT-2003 (87)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: = 500 -
EC50: > 500 -
EC100: > 500 -

Method: other
Year: 1988
GLP: no
Test substance: no data

Test condition: Method: Acute Toxicity for Daphnia, EEC Directive 79/831, March 1989.
23-OCT-2003 (87)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: >= 1000 -
EC0: >= 1000 -
EC50: > 1000 -
EC100: > 1000 -

Method: other
Year: 1986
GLP: no data

Test condition: 10 animals in 250 ml di test solution at different chemical concentrations at 20°C in fresh water. No aerated test. The duration of test was 48 h; after 24 h the EC values were equal to 48 h.
Test substance: DMAC at purity of 99% (Ega-Chemie)
23-OCT-2003 (2)

Species: Mysidopsis bahia (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: = 320 -
LC50 : = 966 -

Method: other
Year: 1986
GLP: no data

Result:

Time	LC50*	LC0	LC100
h	mg/l	mg/l	mg/l
24	3367	1000	>1800
48	1794	560	>1800
72	1198	560	>1800
96	966	320	>1800

*=predicted

Test condition: 10 animals each in about 20 ml of test solution at different chemical concentrations at 20°C and a salinity of 2.8%. No aerated test. The duration of the test was 96 h and the test medium was renewed once a day.
Test substance: DMAC at purity of 99% (Ega-Chemie)
24-MAR-2004 (2)

Species: other aquatic crustacea: Chaetogammarus marinus
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: >= 1000 -
LC50 : > 1000 -

Method: other

Year: 1986
GLP: no data

Result:

Time	LC50	LC0	LC100
h	mg/l	mg/l	mg/l
24	>1000	>=1000	>1000
48	>1000	>=1000	>1000
72	>1000	>=1000	>1000
96	>1000	>=1000	>1000

Test condition: 10 animals in 1000 ml of test solution at different chemical concentrations at 15°C and a salinity of 2.8%. No aerated test and the medium was renewed once a day The duration of the test was 96 h .
Test substance: DMAC at purity of 99% (Ega-Chemie)
24-MAR-2004 (2)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: > 500 -
EC90 : > 500 -

Method: other
Year: 1988
GLP: no
Test substance: other TS

Test condition: DIN 38412 Parte 9: Inhibitory test related biomass growth.
23-OCT-2003 (85)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: other
Species: Escherichia coli (Bacteria)
Unit: mg/l Analytical monitoring: no data
MIC: = .425 -

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

Remark: Toxicities of several known toxicants determined by the TOXI-CHROMOTEST are similar to those with cultured mammalian cells, but there was little correlation between MIC
(Minimal Inhibitory Concn.= the concn. of a chemical causing 20% toxicity) and the LD50, which suggest that this test should be used as a tool of primary screening tests for toxicity.
Test condition: The used test was the TOXI-CHROMOTEST which is based on the ability to inhibit the "de novo" synthesis of beta-galactosidase by a rough mutant of Escherichia coli.
23-OCT-2003 (124)

Species: Pseudomonas putida (Bacteria)
Unit: mg/l Analytical monitoring: no data
LOEC : = 4850 -

Method: other
Year: 1986
GLP: no data
Test substance: no data

Test condition: Inhibitory test related to biomass growth.
23-OCT-2003 (86)

Species: activated sludge, industrial
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring: no
EC10: > 1995 -

Method: other
Year: 1980
GLP: no data
Test substance: no data

Test condition: The test was performed with activated sludge from an industrial waste water treatment plant (1 g/l dry weight). For test concentrations of 15 to 1995 mg/l (nominal conc.), a respiration enhancement of up to 47% was observed. No respiration inhibition.
23-OCT-2003 (91)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Remark: No available data
23-OCT-2003

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Remark: no available data
23-OCT-2003

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

Remark: No available data
23-OCT-2003

4.6.3 Toxicity to Soil Dwelling Organisms

Species: Eisenia fetida (Worm (Annelida), soil dwelling)
Unit: mg/cm² filter paper
LC50: .01 - .1

Year: 1984
Test substance: as prescribed by 1.1 - 1.4

Remark: DMAC was found to be very toxic to the earthworm. This test involved 90 chemicals in an attempt to use the earthworm as a marker species to indicate the relative toxicities of chemicals.
23-OCT-2003 (77)

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

Species: other avian: HEN
Endpoint: mortality
Unit: mg/kg bw
ALD : = 12000 -

Year: 1970

Test condition: The administration was i.v. ALD is Approximate Lethal Dose.
23-OCT-2003 (88)

4.7 Biological Effects Monitoring

Remark: No available data
23-OCT-2003

4.8 Biotransformation and Kinetics

Remark: no available data
23-OCT-2003

4.9 Additional Remarks

Remark: No additional remarks
23-OCT-2003

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Value: 3000 - 6000 mg/kg bw

Remark: LD50= 3000 mg/kg
Reference: Von Kreybig, T. et al.(1969). J. Toxicol. Sci., 19(79):1073-1076.

LD50= 6000 mg/kg
Reference: Reported in Du Pont-Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Auclair M. and M. Hameau (1964). Compt. Rend., 158:245-248.

This RANGE includes 9 values. The value reported by the most authors is ca. 5000 mg/kg. This range is considered as slight acute oral toxicity (Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988).
In rats which died from single oral doses of DMAC, death occurred 24 hours after ingestion due to RESPIRATORY FAILURE. Autopsy showed generalized HEMORRHAGES in SEVERAL ORGANS, DEGENERATION of isolated NERVE CELLS, and NECROSIS of LIVER and KIDNEY TISSUES.

Reference: Reported in Du Pont-Haskell Laboratory-Internal DMAC Review, Oct. 1988 from Kafyan V.B. (1971). Zh. Eksp. Klin. Med., 11(1):39-42.
DMAC was administered to groups of six rats at several different doses. The following MORTALITY RATE showing DELAYED TOXICITY was observed at 24 hours and five days later:

DMAC concn.	Period of observation	Dose(mg/kg) 4600	9400	18800
100%	24 h	0/6	5/6	6/6
100%	5 d	3/6	6/6	
50%	24 h	3/6	6/6	
50%	5 d	5/6	-	

Note: 100% indicates undiluted DMAC administration 50% indicates administration of DMAC mixed with water.

Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Weiss L.R. and R.A. Orzel (1967), Toxicol. Appl. Pharmacol., 11:546-557.
04-NOV-2003 (63) (64) (110) (113)

Type: LD50
Species: mouse
Value: = 4620 mg/kg bw

Method: other
Year: 1976

GLP: no data

Remark: A group of 10 animals (5 males and 5 females) was used for each dose level. The chemical was administered orally via a stomach tube. The solvent was diluted as necessary with 0.9% NaCl solution. The animals were observed up to the 7th day after administration.

In the case of DMAC the deaths occurred up to 3 days after administration.

23-OCT-2003 (4)

Type: LD50
Species: rabbit
Value: > 5000 mg/kg bw

Method: other
Year: 1971
GLP: no data

Remark: The chemical was administrered undiluted by stomach tube. The rabbits were fasted for 24 hours prior to testing.

04-NOV-2003 (141)

Type: other: ALD
Species: rat
Value: >= 7500 mg/kg bw

Method: other
Year: 1976
GLP: no data

Remark: The DMAC , as an aqueous suspension, was administered by intragastric intubation. The surviving animals were sacrificed 14 days later. This value is indicated as ALD=Approximate Lethal Dose.
Test substance: DMAC - Solvent Recovery - Lycra Tar Still Residue

23-OCT-2003 (50)

Species: dog

Method: other: BASF test
Year: 1976
GLP: no data

Remark: The DMAC, was administered by intragastric intubation to five males and five females. Doses: 235 , 470, 940 , 1880 mg/kg. All animals died at the highest dose.

23-OCT-2003 (7)

5.1.2 Acute Inhalation Toxicity

Type: LC50
Species: rat
Exposure time: 1 hour(s)
Value: = 8.81 mg/l

Method: other
Year: 1979
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: The 1-h LC50 of DMAC for ChR-CD female rats was 8.81 mg/l and >8.81 mg/l for male rats.
23-OCT-2003 (137)

Type: LC50
Species: rat
Exposure time: 1 hour(s)
Value: = 10.1 mg/l

Method: other
GLP: no data

Remark: Two rats were exposed to 2800 ppm/1 hour (original concentration reported by the author)
23-OCT-2003 (94)

Type: LC50
Species: rat
Exposure time: 7 hour(s)
Value: = 2.08 mg/l

Method: other
GLP: no data

Remark: Two rats were exposed 575 ppm/ 1 hour (original concentration reported by the author); no mortality
23-OCT-2003 (94)

Type: LC50
Species: rat
Value: = 1.47 mg/l

Method: other
GLP: no data

Remark: Two rats were exposed to 406 ppm/ 1 hour (original concentration reported by the author); animals died within 17 hours from the end of exposure; parenchimal liver degeneration
23-OCT-2003 (94)

Type: LC50
Species: mouse
Value: = 7.2 mg/l

Year: 1979

23-OCT-2003 (111)

Type: LC50
Species: mouse
Exposure time: 3.5 hour(s)
Value: = 1.47 mg/l

Year: 1959

Remark: Six mice exposed for 3.5 hours to 406 ppm survived while three died within 16 hours and another died five days later after termination of the exposure. Two mice examined microscopically showed marked DEGENERATION of the LIVER and considerable DEGENERATION of the RENAL TUBULES. The LUNGS

were CONGESTED, and one animal had foci of recent HEMORRHAGE.
23-OCT-2003 (100)

Type: LC0
Species: rat
Exposure time: 8 hour(s)
Value: 12 mg/l

Method: other
Year: 1962
GLP: no data

Remark: No deaths were found in six albino rats after an EIGHT-HOUR EXPOSURE to a CONCENTRATED VAPOR of DMAC at room temperature (12 mg/l at 20°C). This time value records the longest inhalation period which permitted all rats to survive the two-week observation period.

In BASF (Safety Data Sheet-DIMETHYLACETAMIDE-June 1990) the value is indicated as ACUTE INHALATION HAZARD (rats; test results depend on toxicity and volatility): no mortalities after 8 hours exposure to an enriched air with DMAC at 20°C and 50°C.
23-OCT-2003 (129)

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Value: 2100 - 3600 mg/kg bw

Year: 1990

Remark: In rabbits dermal contact produced EDEMA, HYPEREMIA, and acute INFLAMMATION of the SKIN. Sublethal doses produced DEGENERATION of HEART, LIVER, and KIDNEY when lethal doses also produced DEGENERATION of the BRAIN.

Reference: Reported by Du Pont-Haskell Laboratory-Internal DMAC Review, Oct. 1988 from Horn H.J., Hazelton Laboratories, Unpublished Summary of Data, 7/20/59.

Rabbits given single topical (clipped skin) applications of 100, 250, or 500 mg/kg of undiluted material exhibited NO MORTALITY or IRRITATION during the two-week observation period.
Reference: Wiles J.S. and J.K. Narcisse (1971). Am. Ind. Hyg. Assoc. J., 32:539-545.
This RANGE is reported in BASF (DIN 52900) Safety Data Sheet-DIMETHYLACETAMIDE-June 1990. This values showed moderate toxicity by skin absorption (Du Pont-Haskell Laboratory-Internal DMAC Review, Oct. 1988).
04-NOV-2003 (6) (24) (141)

Type: LD50
Species: mouse
Value: = 9600 mg/kg bw
Year: 1979

Remark: Doses of 1000 or 2500 mg/kg of undiluted DMAC applied to

the clipped skin of groups of two mice produced no deaths after 24 or 48 hours. A dose of 5000 mg/kg, however, resulted in death of one of two mice.

23-OCT-2003 (65) (114)

Type: LD50
Species: rat
Value: = 7500 mg/kg bw

Year: 1977

23-OCT-2003 (79)

Type: LD50
Species: guinea pig
Value: < 940 mg/kg bw

Remark: occlusive
23-OCT-2003 (114)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: i.p.
Value: 2000 - 3840 mg/kg bw

Remark: LD50=2000 mg/kg
Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Fassett D.W.- Unpublished Eastman Kodak Co.Data (Ref. from Horn H.J. 1959).

LD50=3840 mg/kg
Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Caujolle F. et al. (1970). Arzneim.-Forsch., 20:1242-1246.

This RANGE includes 4 values reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988.
DMAC was administred intraperitoneally to groups of six rats at three different doses. The following MORTALITY RATE,
which shows a DELAYED TOXICITY was observed:

DMAC concn.	Period of observation	Dose mg/kg 940	1840	3760
100%	24 h	0/6	0/6	6/6
100%	5 d	2/6	6/6	-
50%	24 h	0/6	0/6	6/6
50%	5 d	0/6	1/6	-

Note: 100% indicates undiluted DMAC administration
50% indicates administration of DMAC mixed with water.

Reference: Reported by Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Weiss L.R. and R.A. Orzel (1967), Toxicol. Appl. Pharmacol., 11:546-547.

21-NOV-2003 (69) (96) (98)

Type: LC50
Species: mouse
Route of admin.: i.p.
Value: 2250 - 4190 mg/kg bw

Remark: LD50=2250 mg/kg
Reference: Wiles J.S. and J.K. Narcisse (1971). Am. Ind. Hyg. Assoc. J., 32:539-545.

LD50=4190 mg/kg
Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Caujolle F. et al. (1970). Arzneim.-Forsch., 20:1242-1246.

This RANGE includes 7 values reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988. Intraperitoneal injection into mice of 50% aqueous DMAC caused FATAL DEPRESSION and COMA during the first post treatment. Two deaths were delayed as long as 10 and 11 days (DELAYED DEATH).

Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Davis K.J. and P.M. Jenner (1959). Toxicol. Appl. Pharmacol., 1:576-578.
21-NOV-2003 (62) (95) (141)

Type: LD50
Species: rabbit
Route of admin.: i.p.
Value: >= 1000 mg/kg bw

Method: other
Year: 1971
GLP: no data

23-OCT-2003 (141)

Type: LD50
Species: rat
Route of admin.: i.v.
Value: 1860 - 2640 mg/kg bw

Remark: LD50=1860 mg/kg
Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Horn H.J., Hazelton Laboratories, Unpublished Summary of Data, 7/20/59.

LD50=2640 mg/kg
Reference: Bartsch W. et al. (1976). Arzneim.-Forsch., 26(8):1581-1583.

This test was performed administering the DMAC, diluited with 0.9% NaCl, into the tail vein. This RANGE includes 3 values reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988.
04-NOV-2003 (61) (100)

Type: LD50
Species: mouse
Route of admin.: i.v.

Value: 2320 - 3020 mg/kg bw

Remark: LD50=2320 mg/kg
Reference: Wiles J.S. and J.K. Narcisse (1971). Am. Ind. Hyg. Assoc. J., 32:539-545.
The DMAC was administered into the medial tail vein.

LD50=3020 mg/kg
Reference: Batsch W. et al. (1976). Arzneim.-Forsch., 26(8):1581-1583. The DMAC, diluited with 0.9% NaCl, was administered into the tail vein. The RANGE includes these 2 values.

04-NOV-2003 (11) (141)

Type: LD50
Species: rabbit
Route of admin.: i.v.
Value: 700 mg/kg bw

Method: other
Year: 1971
GLP: no data

Remark: The chemical was injected through the marginal ear vein.

23-OCT-2003 (141)

Type: other: ALD
Species: rabbit
Value: = 8340 mg/kg bw

Year: 1970

Remark: The value is indicated as ALD=Approximate Lethal Dose.

23-OCT-2003 (97)

Type: LC50
Species: dog
Route of admin.: i.v.
Value: > 240 mg/kg bw

Year: 1960

Remark: Intravenous administration to dogs of a 50% solution of DMAC at doses of 472, 945, 1417, and 1890 mg/kg produced little or no toxicity, even at the hightest dosage level. However, a dose of 945 mg/kg of a 100% material produced DEATH from RESPIRATION FAILURE within four minutes. In another study, administration to dogs of single doses of 1890, 2362, or 2835 mg/kg produced STIFFNESS and INCOORDINATION at the hightest level. The major finding was an INCREASED RESPIRATION RATE. All dogs where normal within three hours. BLOOD COUNTS taken a week later were within normal limits.

23-OCT-2003 (68) (74)

Type: LD50
Species: cat
Route of admin.: i.v.
Value: 240 - 470 mg/kg bw

Year: 1964

23-OCT-2003 (78)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Result: not irritating
EC classificat.: not irritating

Method: other
Year: 1990
GLP: no data

Remark: BASF test
Other Test Results:
When tested and classified according to the regulations of the Department of Transportation (Hazardous Materials Regulations, Title 49 CFR, Section 173.240(a), Oct. 1974) three administered solution: DMAC/0.1 N NaOH, DMAC+water (50:50)/0.1 N NaOH, and DMAC (95%) didn't cause corrosion to rabbit skin.

Reference: Jensen A.W. (1977) Du Pont, Haskell Laboratory, Unpublished Data, Reports No. 342/343/344-77-MR No. 2803-001.
No irritation occurred in 100, 250, 500 mg/kg dose groups (undiluted DMAC was applied to the clipped skin).

Reference: Wiles J.S. and J.K. Narcisse (1971). Am. Ind. Hyg. Ass. J., 32:539-545.
Irritation on uncovered rabbit belly = 2 (very slight irritation). This value indicates the least visible capillary injection from the 0.01 ml of the undiluted chemical within 24 hours.

Reference: Smyth H.F. et al. (1962). Am. Ind. Hyg. Assoc. J., 23:95-107.
04-NOV-2003 (5) (42) (129) (129)

Species: guinea pig
Result: irritating

Method: other
Year: 1955
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: DMAC was found to be irritating to intact guinea pig skin when applied as 50% or 25% aqueous solution. A 10% solution caused little or no irritation to intact skin but moderate irritation on abraded skin.
Reference: Lowen W.K. (1955) Du Pont, Haskell Laboratory, Unpublished Data:MR-13 and MR-48.

DMAC was applied to guinea pigs under a suitable cuff and left in contact with the skin for 24 hours. Doses less than 945 mg/kg killed the guinea pigs. DMAC proved to be a strong

skin irritant.
Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Fassett D.W., Unpublished Eastman Kodak Co. Data (Ref. from Horn H.J. 1959).

04-NOV-2003 (38) (47)

Species: mouse
Result: slightly irritating

Method: other
Year: 1971
GLP: no data

Remark: Slight irritation occurred in 2500 and 5000 mg/kg dose groups and no irritation effects on group treated with 1000 mg/kg. The undiluted chemical was applied to clipped skin.

23-OCT-2003 (141)

5.2.2 Eye Irritation

Species: rabbit
Result: irritating
EC classificat.: irritating

Method: other
Year: 1990
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: BASF test
DMAC (undiluted 0.1 ml) produced mild corneal and conjunctival irritation: the treated eyes were normal three to four days later.
Reference: Reported in TOXALL Data Bank from Du Pont-Haskell Laboratory (1984) EPA/OTS Doc.86 - 8900007478.

Two rabbits receiving three drops of a 50% aqueous solution showed severe erythena, lacrimation, and edema.
Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Horn H.J., Hazelton Laboratories, Unpublished Summary of Data, 7/20/59.

Tested on rabbit eyes, DMAC has caused mild reversible corneal injury graded THREE on a scale of 10 where grade 1 indicates at most a very small area of necrosis resulting from 0.5 undiluted chemical in the eye and grade 5 indicates severe burns from 0.005 ml. and grade 10 indicates severe burn from 0.5ml of a 1% solution in water or propylene glycol
Reference : Smyth H.F. et al. (1962). Am. Ind. Hyg. Assoc. J., 23:95-107.
Upon thermal decomposition, DMAC emits fumes which are highly irritating to the eyes and mucous membranes.

04-NOV-2003 (5) (39) (104) (123) (129)

5.3 Sensitization

Type: no data
Species: guinea pig
Result: not sensitizing
Classification: not sensitizing

Year: 1955
Test substance: as prescribed by 1.1 - 1.4

Remark: DMAC is not a skin sensitizer
23-OCT-2003 (99) (101)

5.4 Repeated Dose Toxicity

Species: rat Sex: male
Route of administration: gavage
Exposure period: 9 days over a 2-week period
Frequency of treatment: daily
Doses: 450 mg/kg (group of 6 animals)
Control Group: yes, concurrent no treatment

Year: 1986
Test substance: as prescribed by 1.1 - 1.4

Remark: All the animals survived the test but were RESTLESS and IRRITABLE, especially during the second week. Their rate of weight gain was inferior to that of control animals. 2/3 rats sacrificed after the last treatment showed INACTIVE SPERMATOGENESIS.
24-MAR-2004 (76)

Species: rat Sex: male
Route of administration: gavage
Exposure period: 10 days
Frequency of treatment: daily
Doses: 1500 mg/kg (group of 6 animals)
Control Group: no data specified

Year: 1986
Test substance: as prescribed by 1.1 - 1.4

Result: Two rats (2/6) died after five doses and another (1/6) after six treatments. During treatment, the animals exhibited marked DISCOMFORT, IRRITABILITY, PALLOR, and LOSS of WEIGHT. Several of the rats suffered from severe DIARRHEA. At autopsy, PATHOLOGICAL SIGNS found in the LIVER, KIDNEY, and STOMACH.
04-NOV-2003 (75)

Species: rat Sex: no data
Route of administration: oral feed
Exposure period: 94 days
Frequency of treatment: daily
Doses: 60 mg/kg (groups of 12 animals)
Control Group: no data specified

Year: 1986
Test substance: as prescribed by 1.1 - 1.4

Result: All rats survived, and NO CLINICAL SIGNS OF TOXICITY were observed. The rats appeared to develop a SLIGHT ANEMIA and LEUKOCYTOSIS.
23-OCT-2003 (72)

Species: rat Sex: male/female
Strain: Long-Evans
Route of administration: drinking water
Exposure period: 24 months
Frequency of treatment: daily
Doses: 100, 300, 1000 mg/kg (groups of 140 animals 70/sex/group)
Control Group: yes, concurrent no treatment

Year: 1980
Test substance: as prescribed by 1.1 - 1.4

Result: DMAC intake was calculated for all weeks fo which liquid consumption data were available based upon the nominal concentrations of drinking water solutions presented to the animals. Test substance intake values were quite variable during the first weeks for the high-dose males due to liquid consumption measurement difficulties and decreased palatability. Subsequently, intake values indicates that the intended dose levels were attained for this group of males and throughout the study for all other groups of treated animals.

No treatment-related effect on survival was observed.
No treatment-related ophthalmologic abnormalities were noted.
A slightly greater incidence of ALOPECIA and MEAN BODY WEIGHT LOSS was noted in the 1000 mg/Kg group.
A slight reduction of MEAN BODY WEIGHTS was noted for the 100 and 300 mg/kg males, the 100 mg/kg effect becoming statistically at 61 weeks. The mean ERYTHROCYTE for the 300 and 1000 mg/kg males were slightly elevated at 24 months while ALKALINE PHOSPHATASE levels were lower than control at all intervals.
LIVER WEIGHT parameters were elevated, as compared to control, in all test groups; KIDNEY WEIGHT parameters were increased for 1000 mg/kg males and females when determined at six-months intervals, and for 1000 mg/kg males and females, as well as some 300 mg/kg animals, at final sacrifice. ADRENAL WEIGHT parameters were noted to have increased in all dose level males at six-month interval only.
Histopathological evaluations were conducted on a set of 24 tissues or organ. No treatment-related lesions were noted at all dose-levels and intervals except moderately severe HEMOSIDERORIS was observed in 1000 mg/kg females at final sacrifice. The affected animals showed no bone marrow hyperplasia, extramedullary hematopoiesis, or other histopathologic evidence of anemia. Based on the data presented, it is concluded: that chronic toxicity was observed at high-dose level as evidenced by marked reduction of mean body weights and weight gains, consistent alterations of organ weight parameters in liver, kidneys, and adrenal glands, and increased incidence of spleen hemosiderosis through histopathologic evaluation.

Thus, the HIGHTEST-DOSE-LEVEL of DMAC ADMINISTERED via DRINKING WATER NOT PRODUCING CHRONIC TOXICITY was 300 mg/kg*day.

24-MAR-2004 (102)

Species: rabbit Sex: no data
Strain: other: albino
Route of administration: dermal
Exposure period: 9 days over a 2-week
Frequency of treatment: daily
Doses: 2000 mg/kg undiluted (groups of 6 animals)
Control Group: no data specified

Year: 1984

Result: DMAC was applied to the closely shaved skin. All animals died and showed evidence of an ACUTE HEPATIC NECROSIS upon autopsy. Other aberrant changes included free fluid in the PERITONEAL and THORACIC CAVITIES and slight CONGESTION of the KIDNEY.

04-NOV-2003 (126)

Species: rabbit Sex: no data
Exposure period: 70 days
Frequency of treatment: 2 h/day, 5 d/week (50 exposures)
Post exposure period: 14 days
Doses: undiluted 1890 mg and diluted 2340 mg (4 ml at 61.9%) (groups of 3 animals)
Control Group: no data specified

Year: 1959

Result: DMAC was kept in contact with the unabraded abdominal skin. No mortalities occurred during the course of the study. The undiluited material produced SCALY, DRY, HARDENED, and FESSURED SKIN; the aqueous solution had no effects. Microscopic examination showed INFLAMMATION of the SKIN after termination of the experiment but no other lesions were observed.

24-MAR-2004 (100)

Species: rat Sex: no data
Route of administration: drinking water
Exposure period: unspecified
Frequency of treatment: daily
Doses: no reported
Control Group: no data specified

Year: 1980

Result: NOEL = 0.4 mg/l
This dose for an unspecified time had no adverse effects. Effect of DMAC on white rats revealed that it had moderate toxicity and cumulativeness and did not change water odor, color or taste. This is a Maximum Permissible Concentration (MPC), the limiting index of its sanitary-toxicological noxiousness in the drinking water. Higher doses produced DISTURBANCES in the CENTRAL NERVOUS SYSTEM, DECREASED HEMOGLOBIN, and ERYTROCYTE COUNTS in bloods, LOWERING of CHOLINESTERASE ACTIVITY, and INCREASED ALANINE TRANSAMINASE

ACTIVITY. The MPC of DMAC could be used as the permissible level of its migration from plastics into water in the hygienic evaluation of new polymer materials.

23-OCT-2003 (125)

Species: dog Sex: no data
Route of administration: dermal
Exposure period: 6 weeks for higher doses and 6 months for lower doses
Frequency of treatment: 5 h/day (rinsed off) and 5 days/week
Doses: 95, 299, 945, 3780 mg/kg (groups of 2 animals)
Control Group: yes, concurrent no treatment

Method: other
Year: 1965
GLP: no data

Result: NOEL = 95 mg/kg bw d
The chemical was administered on clipped trunks.
At 3780 mg/kg DEPRESSION, WEAKNESS, ATAXIA, DIARRHEA, WEIGHT LOSS, and JAUNDICE preceded death. LIVER DAMAGE and MILD IRRITATION of the SKIN were observed. Dogs treated with 945 mg/kg survived the 6-month dosing period. Only the DEGENERATION of LIVER and some SKIN IRRITATION were seen. One of the dog treated with 299 mg/kg lost weigh early in the treatment period but recovered. SKIN ULCERATION occurred at 4 months in one dog and healed, although SKIN SCALINESS was present by the end of the 6-month treatment period in both dogs. No clinical signs were observed in dogs given 95 mg/kg. Dogs treated for 6 months showed slightly reticulated CYTOPLASM in HEPATOCYTES and the SKIN was slightly THICKENED or reflected a mild, INFLAMMATORY RESPONSE.

23-OCT-2003 (70)

Species: rat Sex: male/female
Route of administration: inhalation
Exposure period: 2 weeks
Frequency of treatment: 6h/day and 5d/week
Post exposure period: 14 days
Doses: 100, 288, 622 ppm (groups of 10 male and 10 female)
Control Group: yes, concurrent no treatment

Year: 1984
Test substance: as prescribed by 1.1 - 1.4

Result: At 622 ppm, some rats died, severe WEIGHT LOSS was seen, LIVERS were ENLARGED and NECROTIC, LYMPHOCYTE DEPLETION occurred in the THYMUS and SPLEEN, and BONE MARROW was HYPOCELLULAR. INFLAMMATION of the STOMACH, SMALL INTESTINE, and UPPER RESPIRATORY TRACT was observed.
Rats exposed to 288 ppm showed moderate LIVER HYPERTROPHY but recovered within 14 days.
No significant deviations from normal were seen in rats exposed to 100 ppm.
TESTICULAR ATROPHY was observed in two rats exposed to 288 ppm only after the recovery period hence the relationship of DMAC exposure is questionable.
NOEL = 100 ppm

05-NOV-2003 (71)

Species: rat Sex: male

Route of administration: inhalation
Exposure period: 10 times in two weeks
Frequency of treatment: 6 hours/day and 5 day/week
Doses: 2129 ppm (group of 4 animals)
Control Group: no data specified

Year: 1984
Test substance: as prescribed by 1.1 - 1.4

Result: DMAC led to mortality (1/10), INANITION, WEIGHT LOSS, SMALL TESTES and INACTIVE SPERMATOGENESIS.
23-OCT-2003 (126)

Species: rat Sex: no data
Route of administration: inhalation
Exposure period: 6 months
Frequency of treatment: 6 h/day and 5 d/week
Doses: 40, 64.4, 103, 195 ppm (groups of 20 animals)
Control Group: yes, concurrent no treatment

Method: other
Year: 1961
GLP: no data

Result: LOEL = 40 ppm
Repeated exposure to 40 ppm, DMAC produced only marginal histopathological evidence of LUNG irritation. WEIGHT GAIN were decreased in test animals, but MORTALITY was unchanged. At 100 ppm and above, there was significant dose-dependent toxicity, with NASAL and UPPER RESPIRATORY TRACT irritation or inflammation and LIVER damage as predominant findings. Microscopic examination of rats at the 195 ppm level showed CYTOPLASM DISTURBANCE, CHOLANGITIS, PERIANGITIS, and small areas of focal NECROSIS of the PARENCHYMAL CELLS. At the 103 ppm level, 3/5 rats showed significant LIVER CELL DEGENERATION.
23-OCT-2003 (36)

Species: rat Sex: male
Strain: other: Crl:CD BR
Route of administration: inhalation
Exposure period: 10 exposure days in 2 weeks
Frequency of treatment: single 1-, 3-, 6-h exposure and ten 6-h exposure
Post exposure period: no data
Doses: 50, 150, 300 and 500 ppm

Year: 1993
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: Regardless of exposure level, repeated DMAC exposure in rats, resulted in plasma profiles of DMAC and NMAC similar to
those from a single exposure. The dose-dependent nature of the DMAC AUC data and the absence of effects of repeated 300 and 500 ppm DMAC exposure supported a toxicity-driven upper limit of 350 ppm for a chronic inhalation study.
05-NOV-2003 (37)

Species: mouse Sex: male
Strain: other: Crl:CD-1 (ICR) BR

Route of administration: inhalation
Exposure period: 10 exposure days in 2 weeks
Frequency of treatment: single 1-, 3-, 6-h exposure and ten 6-h exposure
Post exposure period: no data
Doses: 50, 150, 300 and 500 ppm

Year: 1993
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: Regardless of exposure level, repeated DMAC exposure in mice, resulted in plasma profiles of DMAC and NMAC similar to those from a single exposure. The dose-dependent nature of the DMAC AUC data and the absence of effects of repeated 300 and 500 ppm DMAC exposure supported a toxicity-driven upper limit of 350 ppm for a chronic inhalation study.
24-MAR-2004 (37)

Species: rat Sex: male/female
Strain: other: Crl: Cd BR
Route of administration: inhalation
Exposure period: 2 years
Frequency of treatment: 5 days/week, 6hr/day
Post exposure period: none
Doses: 25, 100, 350 ppm (87/sex/group)
Control Group: yes, concurrent no treatment
NOAEL: = 25 ppm

Year: 1994
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: Clinical pathology was evaluated at 3,6,12,18,24 months; Interim sacrifice was carried out at 12 months; hepatic cells proliferation was examined at two weeks and three and twelve months.No compound-related effects on survival were observed.
Rats exposed to 350 ppm had lower body weight and/or body weight gain. There were no compound-related adverse effects on the incidence of clinical signs of toxicity. No hematologic changes were observed.
SERUM SORBITOL DEHYDROGENASE ACTIVITY was increased in rats exposed to 350 ppm. SERUM CHOLESTEROL and GLUCOSE CONCENTRATIONS WERE SIGNIFICANTLY HIGHER IN 100 AND 350 PPM FEMALE RATS.
Compound-related morphological changes were observed in the liver. Exposure to 100 or 350 ppm produced increased absolute and/or relative LIVER WEIGHT, HEPATIC FOCAL CYSTIC DEGENERATION, HEPATIC PELIOSIS, BILIARY HYPERPLASIA (350 ppm only), and LIPOFUCSIN/HEMOSIDERIN accumulation in KUPFFER CELLS. Male rats exposed to 350 ppm had higher KIDNEY WEIGHT correlated with the gross and microscopy changes resulting from a compound-related increase in severity of CHRONIC PROGRESSIVE NEPHROPATHY.
No increase in hepatic cells proliferation was seen at any exposure concentration.
05-NOV-2003 (49)

Species: mouse Sex: male/female
Strain: other: Crl:CD-1 (ICR) BR
Route of administration: inhalation

Exposure period: 18 months
Frequency of treatment: 5 days/week, 6hr/day
Post exposure period: none
Doses: 25, 100, 350 ppm (78/sex/group)
Control Group: yes, concurrent no treatment
NOAEL: = 25 ppm

Year: 1994
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: Clinical pathology was evaluated at 3,6,12,18 months; hepatic cells proliferation was examined at two weeks and three and twelve months. No compound-related effects on survival were observed.
There were no compound-related effects on body weight or weight gain at any concentration. There were no compound-related adverse effects on the incidence of clinical signs of toxicity.
No hematological changes were observed.
Compound-related morphological changes were observed in the liver. Exposure to 100 or 350 ppm produced increased absolute and/or relative LIVER WEIGHT (350 ppm female only), accumulation of LIPOFUSCIN/HEMOSIDERIN in KUPFFER CELLS and CENTRILOBULAR SINGLE CELL NECROSIS. Female mice exposed to 350 ppm had an increase incident of BILATERAL, DIFFUSE RETINAL ATROPHY.
No increase in hepatic cells proliferation was seen at any exposure concentration.
24-MAR-2004 (49)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella Typhimurium 1535, 100, 1537, 1538, 98
Concentration: 10, 15, 20, 25 ul/ml
Metabolic activation: with
Result: ambiguous

Year: 1986
Test substance: as prescribed by 1.1 - 1.4

23-OCT-2003 (81)

Type: Ames test
System of testing: Salmonella Typhimurium TA1535, TA1537, TA1538, TA98, TA100
Concentration: 2, 4, 6, 8 and 10 mg/plate
Metabolic activation: with and without
Result: negative

Method: other
Year: 1976
GLP: no data

Test substance: DMAC - Solvent Recovery - Lycra Tar Still Residue
23-OCT-2003 (51)

Type: Ames test
System of testing: Salmonella typhimurium reverse mutation assay

Concentration: 50-5000 ug/plate
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1989
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: It was concluded that DMAC was devoid of mutagenic activity under the conditions of the test.
23-OCT-2003 (67)

Type: Ames test
System of testing: Salmonella Typhimurium TA1535, TA1537, TA1538, TA98, TA100
Concentration: 3, 6, 9, 12, 15 mg/plate
Metabolic activation: with and without
Result: negative

Method: other
Year: 1977
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

23-OCT-2003 (51)

Type: Ames test
System of testing: Salmonella Typhimurium TA97, TA98, TA100, TA1535, TA1537
Concentration: not reported
Metabolic activation: with and without
Result: negative

Year: 1988

23-OCT-2003 (82)

Type: Sister chromatid exchange assay
System of testing: CHO cells
Concentration: 10, 15, 20, 25 ul/ml
Result: ambiguous

Remark: DMAC increases the frequency of sister chromatid exchange in CHO cells in 10 ul/ml from seven to ten, in 15 ul/ml to twelve. In 20 ul/ml, it caused mitotic delay, the chromosomes in the metaphase are shorter. In a dose of 25 ul/ml, it became toxic.
24-MAR-2004 (26)

Type: other: unscheduled DNA Synthesis (UDS)
System of testing: Human diploid fibroblasts
Concentration: 9370 ug/ml
Result: negative

Year: 1981

Remark: Exposure of 3 hours: there was no increase in UDS in cells treated with DMAC.
23-OCT-2003 (53)

Type: other: transgenic mous mutation assay
System of testing: liver tissues
Concentration: no data
Metabolic activation: no data
Result: negative

Year: 1993
Test substance: other TS: 2%DMAC + 10% Emulphor EL620

Remark: Preliminary the mutagenicity of Adozelesin was studied in the Big Blue TM (1acI) transgenic mouse mutation assay. DMAC was used as control substance.
24-OCT-2003 (41)

5.6 Genetic Toxicity 'in Vivo'

Type: Dominant lethal assay
Species: rat Sex: male
Route of admin.: dermal
Exposure period: single application
Doses: 1500 and 3000 mg/kg

Year: 1972

Result: These treatments didn't cause a dominant lethal response.
24-OCT-2003 (107)

Type: Dominant lethal assay
Species: rat Sex: male
Route of admin.: inhalation
Exposure period: 7 h/day for 5 consecutive days
Doses: 0.072, 2.53 (20,700 ppm)
Result: negative

Year: 1981

Result: Any effect upon pregnancy frequence due to DMAC treatment, but reductions in the positive control groups. Corpora lutea graviditatis counts were not reduced in treated group; implantations per pregnancy were unaffected by treatment, while were reduced in positive controls; frequencies of live implantations and live implantations + late deaths followed closely the pattern of total implantations per pregnancy. Early death frequency didn't show differencies between treated and control groups. It was concluded that there was no evidence of effects due to DMAC treatment.
24-MAR-2004 (53)

Type: Dominant lethal assay
Species: mouse Sex: male
Route of admin.: dermal
Exposure period: single application
Doses: 1500 and 3000 mg/kg

Year: 1972

Result: These treatments didn't cause a dominant lethal response
24-OCT-2003 (107)

Type: Dominant lethal assay

Species: mouse Sex: male
Route of admin.: inhalation
Exposure period: 7 h/day for 5 consecutive days
Doses: 0.072, 2.53 (20,700 ppm)
Result: negative

Year: 1981

Remark: There were no effects attributable to DMAC in the dominant lethal test on pregnancy frequency, numbers of corpora lutea or implantations or the frequency of early deaths
24-MAR-2004 (53)

Type: Dominant lethal assay
Species: mouse Sex: male
Route of admin.: i.p.
Exposure period: single injection
Doses: 680 ul/kg (aqueous solution) or 0.1 ml/animals

Year: 1976

Result: These treatments revealed no dominant lethal effect.
24-OCT-2003 (112)

Type: Drosophila SLRL test
Species: Drosophila melanogaster Sex: male
Route of admin.: inhalation
Exposure period: 95 min.
Doses: 0.72 (200 ppm)
Result: negative

Method: other: Sex Linked Recessive Lethal Test
Year: 1981

05-NOV-2003 (53)

Type: Cytogenetic assay
Species: human Sex: male
Route of admin.: other: workers who are in contact with DMAC
Exposure period: no reported
Doses: environmental monitoring: no data specified

Year: 1985

Result: The cytogenetic analysis of the lymphocytes of 20 workers who are in contact with DMAC was performed. The result indicated that there was not a significant increase in the frequency of CHROMOSOME ABERRATION.
24-OCT-2003 (109)

Type: Cytogenetic assay
Species: rat Sex: male/female
Route of admin.: inhalation
Exposure period: 7 h/day for 1 to 5 consecutive days
Doses: 0.072, 2.53 (20, 700 ppm)
Result: negative

Year: 1981

Remark: Rat bone marrow cells were sampled after 6,24 and 48 hours after exposure. The frequencies of chromosomal aberrations

were not increased significantly.
05-NOV-2003 (53)

5.7 Carcinogenicity

Species:	rat		Sex: male/female
Strain:	Fischer 344		
Route of administration:	gavage		
Exposure period:	52 weeks (364 days)		
Frequency of treatment:	daily and 5 days/week (260 doses)		
Post exposure period:	6 months		
Doses:	4 doses: 1-max. dose = MTD(mg/rat)=30 (ca.330 g bw/rat) and 4 levels decreased in range of 0.5 log unit=ca. 0,3,9,30,90 mg/kg		
Control Group:	other		
Method:	other		
Year:	1968		
GLP:	no data		
Test substance:	as prescribed by 1.1 - 1.4		
Remark:	0, 3 mg/kg (m)	6/12 interstitial cell tumor (testes)	
	9 mg/kg (f)	2/12 adenomas (pituitary)	
		1/12 adenomas (adrenal glands)	
		2/12 fibroadenomas (mammarian)	
		1/12 hyperplasia (mammarian)	
	30 mg/kg (m)	5/14 interstitial cell tumor (testes)	
		1/14 mesoteliomas	
		1/14 hyperkeratosis (stomach)	
		1/14 testicular athrophy	
	30 mg/kg (f)	1/15 adenomas (pituitary)	
		1/15 adenocarcinomas(uterus)	
		2/15 polypus(uterus)	
		2/15 hyperplasia (mammarian)	
	90 mg/kg (m)	2/3 interstitial tumor (testes)	
	90 mg/kg (f)	1/3 lymphomas	
Result:	MTD = maximal tolerated dose The critera chosen for the establishment of the MTD took into account the mortality, gain of body weight, and the general condition of the animals. Three control types were used: - using a concurrent substance: versatile carcinogen-N-2-fluorenylacetamide - using the steroid suspending vehicle - untreating the animals. DMAC was NOT CARCINOGENIC in these experiments.		

24-MAR-2004 (34)

Species:	hamster		Sex:
Route of administration:	dermal		
Exposure period:	6 weeks		
Frequency of treatment:	3 days/week		
Doses:	no reported		
Control Group:	yes, concurrent vehicle		
Year:	1980		
Test substance:	as prescribed by 1.1 - 1.4		

Result: DMAC lowered the yields and incidents of total tumors, and particularly advanced tumors promoted by retinyl acetate or croton oil after initiation by 7,12-dimethylbenz(a)-anthracene.
24-OCT-2003 (92)

Species: rat Sex: male/female
Strain: Long-Evans
Route of administration: drinking water
Exposure period: 24 months
Frequency of treatment: daily
Doses: 100,300,1000 mg/kg (n. 70/sex/group)
Control Group: yes, concurrent no treatment

Year: 1980
Test substance: as prescribed by 1.1 - 1.4

Result: The following tissues from each rats were preserved: adrenals, bone marrow (sternal), brain, eye, gonads, heart, colon, duodenum, ileum, kidneys, liver,lung, lymph node (mesenteric), mammary gland, pancreas, pituitary, salivary gland, skeletal muscle, skin, spinal cord, spleen, stomach, thyroid, urinary bladder, uterus/prostate and gross lesions including tissue masses.
All of the above tissues from the high dose and control killed at 12 and 24 months were examined histopatho-logically. Tissues from animals were also the only tissues examined histopathologically from (a) animals in the high-dose and control groups that died or were killed when moribund before the scheduled sacrifice and (b) all animals in the intermediate treatment groups.
There are no lesions related to treatment in rats killed at 12 months and in male rats killed at 24 months or dying during the time between the two scheduled sacrifices. In female rats killed at 24 months or dying after 12 months, the incidence of thymomas was slightly higher in animals given DMAC then in controls. The incidence was 0/50 in the control group, 1/50 (2%) in the 100 mg/kg group, 0/50 in the 300 mg/kg group and 3/50 (6%) in the high-dose group. These tumours, wich occur spontaneously in Long-Evans rats with a somewhat variable incidence, showed no dose-response relationship and are not though to be related to treatment. The significance of the increased severity (5/10) of the hemosiderosis in the female animals receiving the high dose is unclear, in fact the affected animals showed no bone marrow hyperplasia, extrameullary hemapoiesis, or other histopathologic evidence of anemia which might explain the hemosiderosis. This study revealed NO PATHOLOGICAL SIGNS indicative of CARCINOGENESIS. (see section 5.4)
24-MAR-2004 (103)

Species: rat Sex: male/female
Strain: other: Crl:CD BR
Route of administration: inhalation
Exposure period: 2 years
Frequency of treatment: 5 days/week, 6 hr/day
Post exposure period: none
Doses: 25,100,350 ppm (n. 87/sex/group)
Control Group: yes, concurrent no treatment

Year: 1994

Test substance: as prescribed by 1.1 - 1.4

Result: The incidence of hepatic tumors and testicular tumors were similar to control for all exposure concentrations in males and females:
- 4/127 in control group, 3/125 in 25 ppm group, 7/125 in 100 ppm group and 4/126 in 350 ppm group about hepatic tumors
- 8/65 in control group, 6/53 in 25 ppm group, 8/50 in 100 ppm group and 4/62 in 350 ppm group about testicular tumors
In addition, there no compound-related effects on the incidence of other tumours in either sex at any exposure concentration.
The only statistically significant increase in tumour incidence occurred in 350 ppm females with respect to squamous cell papilloma in the stomach (0, 0, 0 and 3,1% for 0, 25, 100, and 350 ppm respectively). This evidence was not considered to be compound related since it was within the range of the historical controls for the animal supplier and, more importantly, since there was no evidence of other lesions known to precede development of compound-induced squamous cell papillomas/carcinomas.
This study revealed that DMAC was NOT ONCOGENIC under the experimental conditions for rats (see also description of same test in section 5.4.).
Therefore, the no-observed-adverse-effect level (NOAEL) for oncogenicity was 350 ppm.

05-NOV-2003 (49)

Species: mouse Sex: male/female
Strain: other: Crl:CD BR
Route of administration: inhalation
Exposure period: 18 months
Frequency of treatment: 5 days/week, 6 hr/day
Post exposure period: none
Doses: 25,100,350 ppm (n. 78/sex/group)
Control Group: yes, concurrent no treatment

Year: 1994
Test substance: as prescribed by 1.1 - 1.4

Result: Exposure of mice to DMAC for 18 months did not cause a compound-related increase in tumors.
The incidence of hepatic tumors and testicular tumors were similar to control for all exposure concentrations in males and females:
- 16/127 in control group, 20/128 in 25 ppm group, 14/127 in 100 ppm group and 13/130 in 350 ppm group about hepatic tumors
- 0/64 in control group, 0/30 in 25 ppm group, 1/39 in 100 ppm group and 1/65 in 350 ppm group about testicular tumors
The only statistically significant increase in tumour incidence occurred in 350 ppm females with respect to lymphoma (5, 2, 5 and 15% for 0, 25, 100, and 350 ppm respectively). The historical control range for lymphoma at this laboratory is 3.3 to 23.8%, and the average incidence for historical controls is 15.5%. Since the incidence of lymphoma in 350 ppm females is nearly identical to the average incidence of the historical controls, and a dose-relationship was not present, it was not considered to be a compound-related effect.

This study revealed that DMAC was NOT ONCOGENIC under the experimental conditions for mice (see also description of same test in section 5.4.).
Therefore, the no-observed-adverse-effect level (NOAEL) for oncogenicity was 350 ppm.

24-MAR-2004 (49)

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species:	rat	Sex: female
Strain:	Sprague-Dawley	
Route of administration:	inhalation	
Exposure period:	10 days from 6 to 10th day of gestation	
Frequency of treatment:	6 hr/day	
Doses:	32,100, 382 ppm (groups of 25 animals)	
Control Group:	yes, concurrent no treatment	

Method: other
Year: 1991
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: NOEL Maternal toxicity = 100 ppm
NOEL Teratogenicity = 100 ppm
At 282 ppm, both MATERNAL WEIGHT gain during the exposure period and FETAL WEIGHT were significantly decreased and accompanied by a significant dose-response trend. These effects were not seen at doses of 32 or 100 ppm. FETAL RESORPTIONS were not increase in any of the groups exposed to DMAC. Fetal incidents of external, visceral, or skeletal variations and malformations were similar between the test and control groups. Therefore, both fetal and maternal toxicity were noted at 282 ppm and the no-observed adverse-effects level under these experimental conditions was 100 ppm for both the dam and the conceptus. DMAC was not demonstrated to produce MALFORMATIONS in the RAT FETUS at a level that was toxic to the dam. In a pilot dose finding study, exposure of three pregnant dams to 625 ppm was reported to be toxic to the dams and to cause almost COMPLETE RESORPTION of the conceptus but no details are reported.
Test substance: DMAC at purity of 99.9%
24-MAR-2004 (130)

Species:	rat	Sex: female
Strain:	Sprague-Dawley	
Route of administration:	drinking water	
Exposure period:	14 days from 6th to 19th day gestation	
Frequency of treatment:	daily	
Duration of test:	until 20th day of gestation	
Doses:	65,160,400 mg/kg single does by gavage (groups of 22-25 animals)	
Control Group:	yes, concurrent no treatment	

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

Result: NOEL Maternal Toxicity = 65 mg/kg bw
NOEL Teratogenicity = 160 mg/kg bw
No treatment-related effects were observed in the dams in SURVIVAL, APPEARANCE, or BEHAVIOUR at NECROPSY, though animals an all groups including controls had evidence of VIRAL INFECTION which may have compromised the study. Mean MATERNAL BODY WEIGHT gain was reduced significantly only at the 400 mg/kg/day level (p<=0.05) and at 160 mg/kg bw/day a slight reduction in body weight was apparent in the 0- to 20 day interval adjusted weight FETOTOXICITY manifested by increased POSTIMPLANTATION LOSS was seen at the 400 mg/kg/day level while reduction in mean FETAL BODY WEIGHTS was noted at the 160 and 400 mg/kg/day test levels. Developmental variations (REDUCED OSSIFICATION and UNOSSIFIED SKELETAL variations) were increased at the 400 mg/kg/day test level and corresponded to the reduced FETAL BODY WEIGHTS which were observed. Treatment-related MALFORMATIONS of the HEART, major VESSELS and ORAL CAVITY, and ANASARCA were seen at the 400 mg/kg/day DMAC level. No TERATOGENIC EFFECT of DMAC treatment was observed at or below dosage levels of 160 mg/kg/day.
05-NOV-2003 (43)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: gavage
Exposure period: 7-21 of gestation
Frequency of treatment: daily
Duration of test: 22th day of pregnancy
Doses: 20, 65, 150 400 mg/kg (groups of 24-25 animals)
Control Group: yes, concurrent no treatment

Method: other
Year: 1997
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOEL Maternal Toxicity = 65 mg/kg bw
NOEL Teratogenicity = 65 mg/kg bw
Significant, adverse maternal and developmental toxicities were produced at 400 mg/kg. There were significant dose-related reductions in MEAN MATERNAL BODY WEIGHT, WEIGHT GAIN, and FOOD CONSUMPTION.
Developmental toxicity was evident as increased EMBRYOLETHALITY, DECREASED MEAN FETAL WEIGHT, increase fetal malformations and slightly increase fetal variations (including DELAYED OSSIFICATION OF THE SKULL BONE and STENEBRAE).
The majority of the malformations were of the head (SYNOTHIA, NARIS ATRESIA, MICROGNATHIA, CEREBRAL VENTRICLE DISTENSION), cardiovascular system (affecting the HEART AND GREAT VESSELS, PULMONARY ARETRY and VSD).
Minimal developmental toxicity was seen at 150 mg/kg.
No evidence of MATERNAL OR DEVELOPMENTAL TOXICITY was seen at either 65 or 20 mg/kg.
05-NOV-2003 (23)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: dermal
Exposure period: once at 9th day and twice at 10 and 11th (or 12 and

13 days)
Frequency of treatment: once or twice in 48 hours
Doses: 600,1200,2400,4800 mg/kg total (groups of 7 or 8 animals)
Control Group: yes, concurrent no treatment

Year: 1973
Test substance: as prescribed by 1.1 - 1.4

Result: A significant incidence of EMBRYOMORTALITY was found at dosage levels that did not significantly affect the maternal body weight (>5%) during the time of application or show any other clinical signs of toxicity. Application of DMAC on gestation days 12 and 13 was less embryolethal than when applied on days 10 and 11. TERATOGENIC EFFECTS (3/34 fetuses with ENCEPHALOCELE; 1/8 DIFFUSE SUBCUTANEOUS EDEMA) were found only when DMAC was applied on gestation days 10 and 11 at a total dose of 2400 mg/kg (1/3th ALD) (included the dose 1200 mg/kg pro time).
24-OCT-2003 (133)

Species: rabbit Sex: female
Strain: Himalayan
Route of administration: inhalation
Exposure period: from 7th to 19th day of gestation
Frequency of treatment: 6 h/day
Duration of test: until 29th day of gestation
Doses: 0.2, 0.7, 2 mg/l (57,200,570 ppm)(groups of 15 animals)
Control Group: yes, concurrent no treatment

Year: 1989
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: NOEL Maternal Toxicity = 2 mg/l
NOEL Teratogenicity = .7 mg/l
No treatment-related effect on MATERNAL TOXICITY was observed. A slightly greater incidence of fetus malformations was noted in higher dose group and were related overall at HEART, ORAL CAVITY, failure PUPILLARY REFLEX, AGENESIA or HYPOPLASIA of the SPLEEN, STERNAL VERTEBRAE and RIBS. Developmental variations (REDUCED OSSIFICATION) were increased significantly at the 2 mg/l/day test level and corresponded to the reduced FETAL and PLACENTA WEIGHTS which were observed. In the top dose group only there was an increase in HEART AND GREAT VESSEL MALFORMATIONS which was not statistically significant but concurrent and historical control values (4 fetuses with ventricular septal defects and 2 with great vessel malformations in the dose group compared with 2 fetuses with ventricular septal defect in the controls).
No TERATOGENIC EFFECT of DMAC treatment was observed at below dosage levels of 0.7 mg/l/day.
24-MAR-2004 (9)

Species: rabbit Sex: female
Strain: other: Russian
Route of administration: other: Oral (gavage)
Exposure period: from 6th to 18th day of gestation
Frequency of treatment: daily

Duration of test: 28th day postmating
Doses: 94, 282, 470 mg/kg bw (groups of 10-11 animals)
Control Group: yes, concurrent no treatment

Year: 1980
Test substance: as prescribed by 1.1 - 1.4

Result: NOEL Teratogenicity = 94 mg/kg bw
The top dose level was very toxic to the dams with MATERNAL MORTALITIES and all IMPLANTATION WERE RESORBED.
At 282 mg/kg bw and at 94 mg/kg bw there was reduced FOOD INTAKE AND BODYWEIGHT gain in the dams, a nonsignificant increase in resorptions, and reduced number of live fetuses per litter. Fetal weight reduced and 5 fetuses had malformations, 4 with CLEFT PALATE, and one FUSED RIBS and MICROPHTHALMIA.
05-NOV-2003 (55)

Species: rabbit Sex: female
Strain: other: New Zealand White
Route of administration: dermal
Exposure period: from 6th to 18th day of gestation
Frequency of treatment: daily
Duration of test: 29th days
Doses: 120,250,500 mg/kg
Control Group: no data specified

Year: 1973
Test substance: as prescribed by 1.1 - 1.4

Result: NOEL Maternal Toxicity = 500 mg/kg bw
NOEL Teratogenicity = 250 mg/kg bw
No treatment-related effects on MATERNAL TOXICITY were Observed at any test level or progeny effects at the two lower levels.
Developmental alterations were observed at high test level: 1 fetus with UMBILICAL HERNIA, 1 fetus with CYCLOPY, reduced FETAL BODY WEIGHT, increased DEVIATIONS of STERNUM.
05-NOV-2003 (89)

Species: rabbit Sex: female
Strain: other: New Zealand White
Route of administration: dermal
Exposure period: from 8 post-insemination (p.i.) to day 16 (p.i.)
Frequency of treatment: daily dose
Doses: 200 mg/kg bw (1/25th ALD)
Control Group: no

Year: 1977
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: NOEL Teratogenicity = 200 mg/kg bw
No embryotoxic effects were found in rabbits given a total dose of 1800 mg/kg (given in 9 days,from 8 to 16th day of gestation at dose of 200 mg/kg bw d) equal to 1/3 of the skin ALD.Maternal weight was not measured. There was no embryomortality and fetal weight was greater than controls. No malformations were observed.
05-NOV-2003 (133)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: other: embryo culture
Exposure period: from day 9,5 of gestation to 48th in culture
Duration of test: 48 hours
Doses: 0,85-1,75-3,5-5 mM

Method: other: embryo culture (WEC)
Year: 1999
GLP: no data
Test substance: other TS

Remark: NOEL Teratogenicity = 0,85 mM
Result: Using the post implantation rat whole embryo culture (WEC) method, the direct embryotoxic effects of DMAC and its main metabolite (MMAC) have been investigated. Both chemicals showed specific EMBRYOTOXIC and TERATOGENIC EFFECTS at similar concentration levels. The NOEL was 0,85 mM. Macroscopically, the main target organs were SOMITES, BRAIN, and BRANCHIAL BARS. Histological examination revealed an increased in CELL DEATH at the effective concentration on the NEUROEPITHELIUM and BRANCHIAL BARS MESENCHYME. The authors suggest that it may be a matter of discussion whether the TLV value (10 ppm corresponding to 5.4 mg/kg bw/day) is enough for an adeguate protection of female workers
Test substance: as prescribed by 1.1-1.4 and N-MMAC
24-OCT-2003 (54)

5.8.3 Toxicity to Reproduction, Other Studies

Type: other: Fertility
Species: rat
Strain: Sprague-Dawley Sex: male/female
Route of administration: inhalation
Exposure period: 12 weeks for males- until 21th day of gestation and then from 4th day postpartum until 21th day for females
Frequency of treatment: 6 hr/day and 5 days/week premating ---6h/day and 7days/week
Doses: 30, 100, 300 ppm (groups of 10 males & 20 females)-300 ppm (only males)-300 ppm (only females
Control Group: yes, concurrent no treatment

Method: other
Year: 1986
GLP: no data

Remark: Premating Exposure Period
male 10 weeks
female 10 weeks
Result: No compound-related effects on BODY WEIGHT, SURVIVAL, and CLINICAL SIGNS were detected in parenteral rats. NO SIGNIFICANT DIFFERENCES were observed between control and test rats with respect to MATING PERFORMANCE, FERTILITY,LENGHT of GESTATION, PROGENY NUMBERS, STRUCTURE, and VIABILITY. At 21 days post partum, pups derived from mating involving exposure of both sexes to 300 ppm or exposure of parental females to 300 ppm had LOWER BODY WEIGHTS and evaluation of LIVER and GONAD WEIGHT data did not reveal any DMAC-related changes. It is concluded that

the REPRODUCTION in rats was not altered by repeated exposure to up to 300 ppm DMAC.
NOEL Parental = 100 ppm
NOEL F1 Offspring = 300 ppm
Test substance: DMAC at purity of 99.9%
05-NOV-2003 (30)

Type: other: Fertility
Species: rat
Strain: Sprague-Dawley Sex: male
Route of administration: inhalation
Exposure period: 69 days
Frequency of treatment: 6 hr/days and 5 days/weeks
Duration of test: 12 weeks
Doses: 40,116,386 ppm (groups of 12 males)
Control Group: yes, concurrent no treatment

Method: other
Year: 1989
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Premating Exposure Period
male = 43 days
female = 0 days
Result: The exposure of the male rats to DMAC appeared to cause treatment-related effects at 120 and 400 ppm (increased LIVER WEIGHT and LIVER/BODY WEIGHT RATIO). This effect can be explaned with the induction of hepatic enzymes and increase of protein synthesis.
There was no adverse effect on testes weight or hystopathology. The data on REPRODUCTIVE PERFORMANCE (COPULATION and PREGNANCY) indicate no significant differences between any of the treatment groups and the control one. There were no treatment-related embryotoxic or fetotoxic effects obtained in females mated with male rats exposed to DMAC.
NOEL Parental = 40 ppm
NOEL F1 Offspring <= 386 ppm
05-NOV-2003 (136)

Type: other: fertility
Species: mouse
Strain: no data Sex: male
Route of administration: inhalation
Exposure period: 5 days
Frequency of treatment: 7hr/day
Duration of test: 6 weeks
Doses: 0.07, 2.53 mg/l (20, 700 ppm)
Control Group: yes, concurrent no treatment

Method: other: sperm abnormality test
GLP: no data
Test substance: other TS: DMAC, no data on purity

Remark: Premating Exposure Period
male: no mating
female: no mating
Result: Groups of 10 male mice were exposed to the test substances for 5 consecutive days. No clinical signs of toxicity and no

effects on body weight gain were observed. Sperm was examined 5 weeks after the end of exposure. No significant differences in frequency of abnormal sperm between the exposed groups and controls were observed

05-NOV-2003 (29)

5.9 Specific Investigations

5.10 Exposure Experience

5.11 Additional Remarks

Type: Metabolism

Remark: Two RATS each were INTUBATED with 33 or 92 mg of radiolabeled DMAC in corn oil. After 72 hours, 93% of the radiocarbon was in the urine, 5% in the feces, 2% in the tissues and <1% as CO2. The major urinary components were: 60-70% MMAC, 7-10% N-hydroxymethylacetamide, 7-10% acetamide. Some residual DMAC was also recovered in the urine. The major metabolic pathway of DMAC "in vivo" in rats is sequential N-demethylation and elimination from the body. A small proportion of DMAC and its intermediates was hydrolyzed and eliminated as carbon dioxide.

24-OCT-2003 (106)

Remark: Twenty male RATS were given two SUBCUTANEOUS INJECTIONS of 300 mg DMAC on two successive days. Urine samples were collected for a 72-hour period after the first injection.
MMAC and acetamide were identified by gas and thin layer chromatography. Metabolic transformation proceeds via a selective demethylation.

05-NOV-2003 (108)

Remark: 3 male RATS were EXPOSED to ATMOSPHERE containing 5 ppm of 14C-DMAC for 12 hours and were examined during a 60-hour post-exposure period. The primary route of elimination of 14C-DMAC derived radioactivity was in the urine (41% of total recovered 14C), then in the feces and expired air (14 and 15% of total 14C, respectively). At the end of post-exposure period, the carcass and tissues contained about 22% of the total 14C. Fat and muscles were major sites of retention.

24-MAR-2004 (105)

Remark: 20 RATS had 20-80% DMAC solutions (0.12 ml) APPLIED to their BACKS. 24-hour urine samples were collected over the next 3 days. The amount of MMAC increased as the solution concentration increased. Recovery ranged from 13% for the 20% solution to 42% for undiluted DMAC. MMAC was found in the urine 72 hours after application.

05-NOV-2003 (106)

Remark: Whole body inhalation exposure to DMAC where conducted with male rats. Exposure concentration were 50, 150, 300 and 500 ppm. The exposure routine consisted of single 1-,3-,6-h exposure and ten 6-h exposure. Area under plasma concentration curve (AUC) values were detected for DMAC and its metabolite N-methylacetamide (NMAC). DMAC plasma half-life in rats ranged from 0,6 to 1,5 h. The AUC values for DMAC increase 5-fold and 3 fold as exposure concentrations increased from 150 to 300 ppm and 300 to 500 ppm, rispectively. NMAC persisted in plasma for at least 24h after the 150, 300 and 500 ppm exposure. Regardless of exposure level, repeated DMAC exposures resulted in plasma profiles of DMAC and NMAC similar to those from a single exposure.

05-NOV-2003 (37)

Remark: Whole body inhalation exposure to DMAC where conducted with male mice. Exposure concentration were 50, 150, 300 and 500 ppm. The exposure routine consisted of single 1-,3-,6-h exposure and ten 6-h exposure. Plasma profiles indicated mice metabolized DMAC rapidly with plasma half-lives from 0,3 to 0,5 for DMAC. The DMAC AUC values for mice were underestimated due to the required time (<30 min) between termination exposure and the initial blood sample. NMAC was not detected in plasma for mice beyond the 12-h post-exposure timepoint for the 300 and 500 exposure. Regardless of exposure level, repeated DMAC exposures resulted in plasma profiles of DMAC and NMAC similar to those from a single exposure.

05-NOV-2003 (37)

Result: The microsomal metabolism of the test substance (DMAC) and its effects on drug metabolizing enzymes of rat liver were investigated. Male Sprague-Dawley rats were injected intraperitoneally with DMAC in a saline solution at doses of150 and 300 mg/kg/d for 3 days or with other inducers. After sacrifice, the livers were excised, microsomes were prepared and assayed for enzymatic activity.
DMAC treatment did not alter any microsomal monooxygenase orphase II enzymatic activity. The oxidative metabolism of DMAC with control and induced microsomes resulted in the dealkylation of the test substance, giving rise to formaldehyde. Ethanol- or acetone-induced microsomes demethylated DMAC with a vmax higher than that of control microsomes. In a reconstituted system, the purified P4502E

05-NOV-2003

Type: Biochemical or cellular interactions

Result: In cell cultures, DMAC induced rapid, extensive differentiation in a series of embryonal carcinoma cells. DMAC and acid retinoic were effective in inducing differentiation of PCC4 azal embryonal carcinoma tumors grown in mice by s.c. transplantation. Differentiation was associated with DECREASED TUMOR GROWTH RATE, DECREASED MITOTIC INDEX, DECREASED EXTENT of NECROSIS, and INCREASEDSURVIVAL TIME of the HOSTS.

In 4/18 cases,long-term survival of the hosts was effected by a complete differentiation of the malignant embryonal carcinoma tumors into benign teratomas. Retinoic acid/DMAC was effective when administered systemically (i.p. or s.c.) as well as when injected directly into the tumor.

05-NOV-2003 (122)

Type: other: skin penetration

Result: A procedure for measuring the steady state rate of permeation of several commercial solvents through living human skin (obtained from healthy females) was developed. Permeation was measured using a Franz Diffusion Cell, a two-chember cell with a water jacket and magnetic stirrer inthe collection area; water temperature was 37 degrees Centigrade; the resulting skin temperature was 34 degrees Centigrade. The area of exposed skin was 0.64 cm2. According to the authors, the determined permeability rate of the test substance was 107 g/m2/h.
Source: BASF AG Ludwigshafen
Test substance: N,N-dimethylacetamide; according to the authors, the compound was of the highest available commercial quality.

05-NOV-2003

Type: other: Experience with Human Exposure

Remark: Biological Monitoring for Dimethylacetamide: Measurement for 4 Consecutive Weeks in a Workplace. The determination of URINARY MMAC in the end-of-shit urine was used to monitor exposure to DMAC. 5 workers were observed followed for 4 consecutive weeks. Airborne DMAC appeared to account for the greatest amount of urinary MMAC detected and, at the exposure concentrations encountered (0.5 to 2 ppm). A relationship of 10 ppm urinary MMAC for each 1 ppm DMAC inhaled was observed. Mean airborne DMAC concentrations were somewhat higher by the end of the week, but the magnitude was such that changes in DMAC exposures can be quantitatively reflected by urinary MMAC.

05-NOV-2003 (44)

Remark: Sulla patologia professionale da Dimetilacetamide

41 workers, who had been working from 2 to 10 years in the spinning department, were examined. The absorption routes are per skin and inhalation via. The symptoms most frequently complained of and the signs observed were indicated of LIVER INVOLVEMENT. Moreover in numerous cases troubles of BRONCHI and of the UPPER RESPIRATORY TRACT, GASTRIC and NERVOUS TROUBLES, and JOINT PAINS were also present. The BROMSULPHALEIN EXCRECTION TEST (BET) was the most sensitive, demostranting LIVER IMPAIRMENT in 63% of the cases (19/30) and establishment a clear relationship between LIVER IMPAIRMENT/DMAC EXPOSURE DURATION (<1 year 11,4% workers with slow BET, 2-7 years 50%, and 7-10 years 90%). The conclusion is drawn that DMAC has a HEPATOTOXIC ACTION, though relatively moderate, in men occupationally exposed. DMAC airborn levels are not reported.

24-MAR-2004 (15)

Remark: Dimethylacetamide: A Hitherto Unrecognized Hallucinogenic Agent. This chemical produced a abnormal mental state when the dosage reached a critical value of 400 mg/kg bw/day for 3 days or more. Striking hallucinations appeared within 24 hours, subsiding over the next few days. Corresponding encephalographic changes were noted.

05-NOV-2003 (139)

Remark: HUMAN THRESHOLD

ODOR THRESHOLD
for 50% response is 21.4 ppm, for 100% response 46.8 ppm.
Reference: Reported in HSDB-Data Bank from ACGIH (1980). Documentation of the threshold limit values. 4th Ed., Cincinnati, Ohio:145.

Probable ORAL LETHAL DOSE: 0.5-5 g/kg
Reference: Reported in HSDB-Data Bank from Gosselin R.E. et al. (1976). Clinical toxicology of commercial products-Part II 4th Ed., Eds.: Williams & Wilkins, Baltimore:135.

IDLH (Immediat. Danger. to Life/Health): 400 ppm
Reference: Reported in HSDB-Data Bank from NIOSH (1987). Pocket guide to chemical hazards-Publ. No. 85-114. U.S. Dept. of Health and Human Services, February 1987:106.

Out-door air limit value (Human Health): 0.1 mg/m3
Reference: Danish PA

24-MAR-2004

Remark: Environmental and Biological Monitoring of Workers Occupationally Exposed to Dimethylacetamide

Exposure to DMAC was measured in a plant where a prefabricated synthetic product was handled and mechanically processed. Stationary monitoring, personal ambient monitoring, and biological monitoring were employed to evaluate exposure. Personal exposure in the breathing zone varied considerably in comparison with a relatively constant level observed with stationary monitoring. No correlation between personal airborne exposure and excretion of MMAC in urine was detected during a full workshift (5 days). Most workers studied (6/8) excreted about 13% of the calculated inhaled dose as metabolite in urine. For two workers this parameter was about 30%. It is concluded that for DMAC, which is easily absorbed through the skin, biological monitoring is superior to airborne concentration monitoring in determining total uptake and (possible) health risk.

24-MAR-2004 (12)

Remark: A PHASE I STUDY OF DIMETHYLACETAMIDE

DMAC was given to 17 patients as a possible cancer chemotherapeutic agent. Injection of the DMAC i.v. as a 10% solution at 100 mg/kg/day for 5 consecutive days, then

gradually increased to 400-500 mg/kg/day for 4 to 5 days caused severe NAUSEA and VOMITING which occurred whithin 14 hours of administration. TOXICITY to LIVER, illustrated by SGOT levels was shown in 7/17 patients on 400 mg/kg for at least 3 days. The primary manifestation of DMAC toxicity appeared as ALTERED CNS FUNCTION. Those 15 patients surviving long enough to be evaluate developeda distinctly ABNORMAL MENTAL STATE (LETHARGY, CONFUSION, DISORIENTATION, ALLUCINATIONS, DELUSIONS) when the dosage reached 400 mg/kg for 3 days or more. The delay of this effect doesn't suggest a direct action by DMAC itself.

05-NOV-2003 (140)

Remark: ACGIH (1994-1995) recommends to determine the content of N-methylacetamide in the urine of workers at the end of shift at end of workweek to monitore the occupation exposure.
The BEI must be 30 mg/g creatinine.

24-MAR-2004

Remark: Mortality from tumors in workers in an acrylic fiber factory

A retrospective epidemiological cohort study of mortality was undertaken in 671 workers with at least 12 months exposure to acrilonitrile (AN), 571subjects had simultaneous exposure to dimethylacetamide (DMAC). Observed mortality in the cohort was compared with expected mortality, calculated on the basis of the mortality rates of the general population. A statistically significant excess was found in the mortality rate from intestinal and colon tumors (SMR = 10.5, 4 observed). However, this finding was significant only in subgroup with 1 to 4 years exposure or 1 to 9 years latency. It is therefore concluded that there is no relationship AN and /or DMAC exposure and mortality from tumors of the colon
and intestine.

05-NOV-2003 (52)

Remark: Monitoring Acrylic Fiber Worker for Liver Toxicity and Exposure
To Dimetthylacetamide
2. Serum Clinical Chemistry Results of
Dimethylacetamide-Excposed Workers
Worker exposure to N,N-dimethylacetamide (DMAC) in acrylic fiber plant was measured, for 1 year study period, by full-shift (12 h) personal air monitoring for DMAC and by biological monitoring for level of DMAC, N-methylacetamide, and acetamide in post-shift spot urine samples. Evidence of liver toxicity was assessed by serum clinical chemistry tests at least once during the study period for all 127 male workers in two study departements and for 217 male in-plant control with no previous or current exposure to DMAC. If a worker's biomonitoring results exceeded one of two "trigger" values established for the study (60 mg MMAC /g creatinine or 136 mg DMAC equivalent/g creatinine), additional serum clinical chemistry tests were conducted at weekly intervals for 3 weeks. DMAC-exposed workers were classified as either high exposure, if one or more biomonitoring

result exceeded one of the trigger values, or unspecified exposure if none of them did. Control-group employees were classified as no-exposure. Mean DMAC in air level for the high and unspecified exposure groups appeared to differ (geometric mean DMAC in air level of 1,9 and 1,3 ppm 12 hours time-weighted average respectively). No significant DMAC exposure-related trends in hepatic serum clinical chemistry were detected. Neither transient increase in serum analyte levels after a "high" biomonitoring result nor an elevated mean level over the study period when compared with in-plant control were observed.
These results suggest that brief threshold limit value-level exposures and cronic low-level exposure do not cause hepatoxic clinical chemistry responses.

05-NOV-2003 (132)

Remark: Dermal absorption of N,N-dimethylacetamide in human volunteers

Twelve healthy male volunteers (mean age 25.2 years, range 21-43 years) were exposed to DMAC for 4 h on two occasions at intervals of 96 h or above to investigate the potential absorption of the solvent vapour, the biological half-life of NMAC in urine as the biological exposure item of DMAC, and the adjustment method for urinary concentrations.
DMAC concentrations were 6.1 ± 1.3 ppm for dermal (whole body with respiratory mask) and for inhalation exposure (nose only). Mean dermal absorption was estimated to be 40,4% of the total DMAC uptake. Biological half-lives of urinary NMAC were 9 + 1.4 h and 5.6 + 1.3 h via skin and lung respectively. Mean NMAC in urine just after 5 consecutive workdays (8 h/day) at 10 ppm DMAC exposure was assumed to be 33.7 mg/g Cr (18.6-70.0 mg/g Cr).
Creatinine-adjusted NMAC concentration in urine for each volunteer within 12 h after the exposure was more closely correlated with the total excretion amount of NMAC up to 36 h than with urinary-volume-adjusted or specific-gravity-adjusted NMAC concentration in both the dermal and inhalation exposure experiments.
DMAC vapor was significantly absorbed through the skin. Estimated NMAC values indicate that 20 mg/g Cr NMAC seems to be appropriate as the biological exposure index.

05-NOV-2003 (58)

(1) ACGIH (1999). Threshold limit values and biological exposure indices. Cincinnati, Ohio, 25 (supplement n.1 - January 2000).

(2) Adema D.M.M. and G.H. van den Bos Bakker (1987) Aquatic toxicity of compounds that may be carried by ships (Marpol 1973, Annex II). A progress report for 1986. Report n. R 86/326a. TNO Netherlands:1-20.

(3) ADR 1.1.95

(4) Bartsch W. et al. (1976). Arzneim.-Forsch., 26(8):1581-1583.

(5) BASF (DIN 52900) Safety Data Sheet - DIMETHYLACETAMIDE-June 1990.

(6) BASF (DIN 52900) Safety Data Sheet-DIMETHYLACETAMIDE-June 1990. (Du Pont-Haskell Laboratory-Internal DMAC Review, Oct. 1988).

(7) BASF AG Unpublished report ZST_ Nr XXIII/236-2. 24 .11.1977

(8) BASF AG (1979) Unpublished report 78/277

(9) BASF AG: Toxicol. Laboratory - Unpublished Data: ZST-No. 90R0104/8638, Gen. 1989.

(10) BASF-Technical Leaflet-Dimethylacetamide-May 1987:M 5304 e.

(11) Batsch W. et al. (1976). Arzneim.-Forsch., 26(8):1581-1583. The DMAC, diluited with 0.9% NaCl, was administered into the tail vein.

(12) Borm P.J.A. et al. (1987). J. Occup. Med., 29:898-903.

(13) Chemical Safety Sheets (1991). Eds.: Kluwer Academic Publ., Samson Chemical Publ., Dutch Institute for the Working Environment, Dutch Chemical Industry Association:337.

(14) CHEMICALS INSPECTION & TESTING INST.-JAPAN. Biodegradation and Bioaccumulation DATA of EXISTING CHEMICALS BASED on the CSCL JAPAN. Published by Japan Chemical Industry Ecology-Toxicology & Information Center, October 1992.

(15) Corsi G.C. (1971). Med. Lav., 62, 28:1-15.

(16) Document on Dmac by Bayer, DuPont, Ertisa, Fisipe, Montefibre, CIRFS (not published 31/08/98).

(17) Du Pont (1988), DIMETHYLACETAMMIDE: Properties, Uses, Storage and Handling. Printed in U.S.A.:1.

(18) Du Pont (1988)- DIMETHYLACETAMIDE: Properties, Use, Storage and Handling. Printed in U.S.A.:2.

(19) Du Pont (1988). DIMETHYLACETAMIDE: Properties, Uses, Storage and Handling. Printed in U.S.A.:22.

(20) Du Pont (1988). DIMETHYLACETAMIDE:Properties,

Uses, Storage and Handling. Printed in U.S.A.-pp.33.

(21) Du Pont (1988). DIMETHYLACETAMIDE:Properties, Uses, Storage and Handling. Printed in U.S.A.:15.

(22) Du Pont (1988). DIMETHYLACETAMMIDE: Properties, Uses, Storage and Handling. (Printed in U.S.A.:11

(23) Du Pont Haskell Labs (1997) (HL-1997-00203). DMAC: Developmental toxicity study in Sprague-Dawley rats. Unpublished data.

(24) Du Pont-Haskell Laboratory-Internal DMAC Review, Oct. 1988 from Horn H.J., Hazelton Laboratories, Unpublished Summary of Data, 7/20/59.

(25) Du Pont-MATERIAL SAFETY DATA SHEET-DMAC-June 1992.

(26) DuPont- Haskell Laboratory - internal DMAC review, Oct. 1988

(27) Dutch Association of Safety Experts (1980). Handling Chemicals Safety.

(28) EU Decision 94/904/CE.

(29) Fairhurst S et al. HSE Criteria document for an OEL, N,N-Dimethylacetamide pub.lished by HMSO C20, London 1992

(30) Ferenz R.L. and G.L. Kennedy (1986). Fundam. Appl. Toxicol., 7:132-137.

(31) Garlanda T. and M. Masoero Garlanda (1990). Distribuzione e trasporto nell'ambiente in funzione delle sue proprieta' chimico-fisiche.
Distribution in the environment - Environmental Partitioning Model: a Computer Program

(32) Gosselin R.E., H.C. Hodge, R.P. Smith and M.N. Gleason (1976). Clinical toxicology of commercial products - Part II 4th Ed., Williams and Wilkins, Baltimore:135

(33) Guzewich DC et al.; Air sampling around a Hazardous Liquid Surface Impoundment. 76th Ann Mtg Air Pollut Contr Assoc paper 24.1 (1983).

(34) Hadidian Z.T. et al. (1968). J. Nat. Cancer Inst., 41(4): 985-1036.

(35) Hawley G.G. (1977). The condensed chemical dictionary. 9th Ed., Van Nostrand Reinhold Co., New York:303

(36) Horn H.J. (1961). Toxicol. App. Pharmacol., 3:12-24.

(37) Hundley S.G. et al. (1994) Toxicology Letters 73, 213-225

(38) Internal DMAC Review, Oct. 1988 from Fassett D.W., Unpublished Eastman Kodak Co. Data (Ref. from Horn H.J. 1959).

(39) Internal DMAC Review, Oct. 1988 from Horn H.J., Hazelton Laboratories, Unpublished Summary of Data, 7/20/59.

(40) Israeli Patent Number 44740,06/15/78 (UpJohn Co.)

(41) IUCLID:Monroe, T.J. and Mitchel. M.A. : Cancer Res, 53, 5690-5696(1993).

(42) Jensen A.W. (1977) Du Pont, Haskell Laboratory, Unpublished Data, Reports No. 342/343/344-77-MR No. 2803-001.

(43) Johannsen F.R. et al. (1987). Fundam. App. Toxicol. 9:550-556.

(44) Kennedy G.L. and J.W. Pruett (1989). J. Occ. Med., 31(1):47-50.

(45) Kim S.N. (1988). Drug Metab. Rev., 19:345-368

(46) Kroschwitz J.I. (Ed.) (1990). Polymer: Fibers and Textiles, A Compendium. J.Wiley & Sons, New York, pp. 867.

(47) Lowen W.K. (1955) Du Pont, Haskell Laboratory, Unpublished Data:MR-13 and MR-48.

(48) Mackinson F.W., R.S. Stricoff and L.J. Partridge Jr. (Eds). (1981). NIOSH/OSHA- Occupational Health Guidelines for Chemical hazards. DHHS(NIOSH) publication No. 81-123 (3 Vols.)-Washington, DC: U.S. Government Printing Office (reported in HSDB-Data Bank).

(49) Malley L.A. et al (1995) Foundamental and Applied Toxicology 28, 80-93

(50) Martin B.E. (1976). Du Pont-Haskell Laboratory-Unpublished Data-Report nø 548-76-MR nø 2427-001 and reported in TOXALL- Data Bank from Kennedy G.L. (1986). Drug Chem Toxicol., 92(2):147-170.

(51) Martin B.E., Du Pont Company Data, Haskell Laboratory, Unpublished Data: Report No. 464-76-MR No. 2389-001.

(52) Mastrangelo et al., (1993). J. Occup. Med., 43 (3) 155-8

(53) Mc Gregor D.F.,Tier II Mutagenic screening of 13 NIOSH priority compounds:DMAC Rep N° 33 1981 PB83-13390-0

(54) Menegola E. et al. (1999) , Toxicology in Vitro, 13: 409-415.

(55) Merkle J. And Zeller H. (1980). Arzneim. Forsch./Drug Research, 30, 9:1557-1562.

(56) Montefibre data and US EPA Use and Exposure profile, 1995

(57) Nellis A.A. (1956). DIMETHYLACETAMIDE. The Chemstrand Co., Alabama: 1-5

(58) Nomiyama T. et al. (2000). Int. Arch.Occup. Environ. Health, vol. 73, n°2, 121-126.

(59) Official Journal of European Communities L 142/48 on 16th

June 2000 Directive n.2000/39/EC on 8th June 2000

(60) Reference: ACGIH (1980). Documentation of the Threshold Limit Values. 4th Ed., Cincinnati, Ohio:145.

(61) Reference: Bartsch W. et al. (1976). Arzneim.-Forsch., 26(8):1581-1583.

(62) Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Caujolle F. et al. (1970). Arzneim.-Forsch., 20:1242-1246.

(63) Reference: Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Weiss L.R. and R.A. Orzel (1967), Toxicol. Appl. Pharmacol., 11:546-557.

(64) Reference: Von Kreybig, T. et al.(1969). J. Toxicol. Sci., 19(79):1073-1076.

(65) Reference: Wiles J.S. and J.K. Narcisse (1971). Am. Ind. Hyg. Assoc.J., 32:539-545.

(66) Report to Montefibre from Biffi (1995). DMAC: Biodegradation by modified MITI test. Biolab Report n. 94/20164:1-8.

(67) Report to Montefibre from May K. (1989). Dimethylacetamide: assessment of muthagenic potential in histidine auxotrophs of Salmonella Typhimurium (the Ames test). LSR Report 89/MTR089/0568:1-28.

(68) Reported by Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Horn H.J., Hazelton Laboratories, Unpublished Summary of Data, 7/20/59.

(69) Reported by Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Weiss L.R. and R.A. Orzel (1967), Toxicol. Appl. Pharmacol., 11:546-547.

(70) Reported by Kennedy G.L. (1986) CRC Crit. Rev. Toxicol., 17:129-182 from Horn H.J. (1961). Toxicol. Appl. Pharmacol. 3:12-24.

(71) Reported by Kennedy G.L. (1986) CRC Crit. Rev. Toxicol., 17:129-182 from Kelly D.P. et al. (1984). Toxicologist, 4:65.

(72) Reported by Kennedy G.L. (1986) CRC Crit. Rev. Toxicol., 17:129-182 from Sherman H., Du Pont, Haskell Laboratory, Unpublished Data:toxicity study, dieting feeding.

(73) Reported by Kennedy G.L. (1986) CRC Crit. Rev. Toxicol., 17:129-182 from Wallen I.E. et al. (1957). Sewage Ind. Wastes, 29:695.

(74) Reported by Kennedy G.L. (1986), C.R.C. Critical Reviews in Toxicology, 17(2):129-182 from Auclair M. and N. Hameau (1964), Compt. Rend., 158:245-248.

(75) Reported by Kennedy G.L. (1986), CRC Crit. Rev. Toxicol., 17: 129-182 from Du Pont, Haskell Laboratory, Unpublished

Data:short-term toxicity.

(76) Reported by Kennedy G.L. (1986), CRC Crit. Rev. Toxicol., 17:129-182 from Du Pont, Haskell Laboratory, Unpublished Data: short-term toxicity..

(77) Reported by Kennedy G.L. (1986). CRC Crit. Rew. Toxicol., 17:129-182 from Roberts B.L. and H.W. Dorough (1984). Environ. Toxicol. Chem. 3(1):67-78.

(78) Reported by Kim S.N. (1988), Drug Metab. Rev., 19:345-368 from Auclair M. and N.Hameau (1964), Soc. Biol., 158:245.

(79) Reported by Kim S.N.(1988). Drug Metab. Rew., 19:345-368 from Stula E.F. and W.C. Krauss (1977), Toxicol. Appl. Pharmacol., 41:35.

(80) Reported in HSDB-Data Bank from Atkinson R. (1987). Int. J. Chem. Kinet., 19:799-828.

(81) Reported in AIDA (13/11/92) - ALSTOFF INFORMATION Date Bank from Satory E. et al. (1986). Acta Pharm. Hung., 56(3):97-108.

(82) Reported in AIDA (13/11/92)- ALSTOFF INFORMATION Date Bank from Zeiger E. et al. (1988). Environm. Molec. Mutagen., 11(suppl. 12):1-158.

(83) Reported in AIDA (13/11/92)-Alstoff Information Data Bank: Cit. in BASF AG Analytical Laboratory-Unpublished Data from Rekker R.F. (1988). The hydrophobic fragmental constant. Elsevier, Amsterdam

(84) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank from BASF AG (1977), Ecological Laboratory-Unpublished Data.

(85) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank from BASF AG (1988), Ecological Laboratory-Unpublished Data.

(86) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank from BASF AG (312186), Analytical Laboratory-Unpublished Data.

(87) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank from BASF AG, Ecological Laboratory-Unpublished Data (1021/88).

(88) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank from Caujolle F. et al. (1970). Arzneim.-Forsch., 20:1242-1246.

(89) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank and in Kennedy G.L. (1986). CRC Crit. Rev. Toxicol., 17:129-182 from Monsanto Co. - Unpublished Data: teratogenic study, rabbits.

(90) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank from Applegate V.C. et al. (1957). Special Sci. Report Fishes, No. 207.

(91) Reported in AIDA (13/11/92)-ALSTOFF INFORMATION Date Bank

from BASF AG (1980). Ecological Laboratory-Unpublished Data.

(92) Reported in AIDA-ALSTOFF INFORMATION Date Bank (13/11/92) from McGaughy C. and J.L. Jensen (1980). Oncology, 37:65-70.

(93) Reported in Du Pont (1988). DIMETHYLACETAMIDE: Properties, Uses, Storage and Handling. Printed in U.S.A.:15 from OSHA Regulations 29 CFR 1910.106: Flammable and Combustible Liquids.

(94) Reported in Du Pont - Haskell Laboratory Internal DMAC Review, Oct. 1988

(95) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Davis K.J. and P.M. Jenner (1959). Toxicol. Appl. Pharmacol., 1:576-578.

(96) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Fassett D.W.- Unpublished Eastman Kodak Co.Data (Ref. from Horn H.J. 1959).

(97) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Caujolle F. et al. (1970), Arzneim.-Forsch., 20:1242-1246.

(98) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Caujolle F. et al. (1970). Arzneim.-Forsch., 20:1242-1246.

(99) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Fassett D.W., Unpublished Eastman Kodak Co. Data (Ref. from Horn H. J. (1959)).

(100) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Horn H.J., Hazelton Laboratories, Unpublished Summary of Data, 7/20/59.

(101) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Lowen W.K. (1955) Medical research Projects MR-13 and MR-48- Unpublished Data.

(102) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Monsanto Chemical Company, Unpublished Data: Report No. BDN-75-61, Project No. 75-1267, January 7, 1980.

(103) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Monsanto Chemical Company, Unpublished Data:Report No. BDN-75-61, Project 75-1267, January 7, 1980.

(104) Reported in Du Pont - Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Weiss L.R. and R.A. Orzel (1967). Toxicol. Appl.Pharmacol., 11:546-557.

(105) Reported in Du Pont, Haskell Laboratory, Internal DMAC Review, Oct. 1988 from Monsanto Chemical Company, Unpublished Data: Report No. ML-80-384, October 21, 1982.

(106) Reported in Du Pont, Haskell Laboratory, Internal DMAC Review, Oct. 1988 - Unpublished Data.

(107) Reported in Du Pont, Haskell Laboratory, Internal DMAC Review, Oct. 1988 from Arnold D. et al. (1972). Industrial Bio-Test Laboratories, Inc., Report IBT-E582A

(108) Reported in Du Pont, Haskell Laboratory, Internal DMAC Review, Oct. 1988 from Barnes J.R. and K.E. Ranta (1972). Toxicol. Appl. Pharmacol., 23:271-276.

(109) Reported in Du Pont, Haskell Laboratory, Internal DMAC Review, Oct. 1988 from Katosova L.D. and G.I. Pavlenko (1985). Mutat. Res., 147:301-302.

(110) Reported in Du Pont-Haskell Laboratory - Internal DMAC Review, Oct. 1988 from Auclair M. and M. Hameau (1964). Compt. Rend., 158:245-248.

(111) Reported in Du Pont-Haskell Laboratory- Internal DMAC Review, Oct. 1988 from Anon. (1979). Zhonghua Yufanggixue Zazhi, 13:39.

(112) Reported in Du Pont-Haskell Laboratory- Internal DMAC Review, Oct. 1988 from BASF, Unpublished Data, 4/6/76.

(113) Reported in Du Pont-Haskell Laboratory-Internal DMAC Review, Oct. 1988 from Kafyan V.B. (1971). Zh. Eksp. Klin. Med., 11(1):39-42.

(114) Reported in Du Pont-Haskell Laboratory-Internal DMAC Review, Oct. 1988 from Anon. (1979). Zhonghua Yufangyixue Zazhi, 13: 29.

(115) Reported in HSDB-Data Bank

(116) Reported in HSDB-Data Bank from Geiger D.L. et al. (Eds.) (1990). Acute toxicities of organic chemical to fathead minnows (pimephales-promelas). Vol. V. Superior WI:133.

(117) Reported in HSDB-Data Bank from Lyman W.J. et al. (1982) Handbook of chemical property estimation methods. NY:McGraw -Hill Chapt. 4, 5 & 15 and from Taft R.W. et al. (1985). Nature, 313:384-386.

(118) Reported in HSDB-Data Bank from NFPA (1978). Fire protection guide on hazardous materials. 7th Ed., Boston, Mass.:325M-82.

(119) Reported in HSDB-Data Bank from Taft R.W. et al. (1985). Nature, 313:384-386.

(120) Reported in HSDB-Data Bank from U.S. Coast Guard, Department of Transportation. CHRIS - Hazardous Chemical Data. Manual 2. Washington, DC: U.S. Government Printing Office, Oct.1978.

(121) Reported in HSDB-Data Bank.

(122) Reported in Kennedy G.L. (1986). CRC Crit. Rev. Toxicol., 17:129-182 from Speers W.C. (1982). Conversion of

malignant murine embryonal carcinomas to benign teratomas by chemical induction of differentiation in vivo. Cancer Res., 43:1843.

(123) Reported in TOXALL Data Bank from Du Pont-Haskell Laboratory (1984) EPA/OTS Doc.86 - 8900007478.

(124) Reported in TOXALL Data Bank from Kamatura M. (1987). Keio Igaku, 64(2):213-220.

(125) Reported in TOXALL-Data Bank from Bogdanov M.V. et al. (1980). Gig. Sanit., (6):76-78.

(126) Reported in TOXALL-Data Bank from Du Pont, Haskell Laboratory (1984). Toxicity studies on DMF and DMAC with cover sheets and letter dated 092484. EPA/OTS:Doc. 86-890000747S.

(127) Responder

(128) SAX- Dangerous properties of Industrial Materials-1989:1333/DOO800.

(129) Smyth H.F. et al. (1962). Am. Ind. Hyg. Assoc. J., 23:95-107.

(130) Solomon H.M. et al. (1991). Fundam. Appl. Toxicol., 16:414-422.

(131) Spectrum of Substance
Rudi Pont (1988). High Purity Solvent Handbook. Printed by HETALAB CHEMICAL CORP., Parsipany, N.J.:143.

(132) Spies G. J., et al (1995). J. Occup. Envir. Med. 1102-1107

(133) Stula E.F. et al.(1973). Du Pont - Haskell Laboratory - Unpublished Data: Pathology Report No. 60-73.

(134) Tonogai Y., Ogawa S., Ito Y. and M. Iwaida (1982). J. Toxical. Sci., 7:193-203

(135) US EPA Use and Exposure Profile, 1995

(136) Wang G.M. et al. (1989). J. Toxicol. Environ. Health, 27:297-305.

(137) Watts J.C. (1978) Du Pont Company Data, Haskell Laboratory, Unpublished Data:Report nø 69-79-MR nø 3025-002.

(138) Weast, R.C. (1979). Handbook of Chemistry and Physics. 60th Ed., CRC Press Inc., Boca Raton, Florida, C-84.

(139) Weiss A.J. et al. (1961). Science, 136:151.

(140) Weiss A.J. et al. (1962). Cancer Chemotherapy Reports, 16: 477-485.

(141) Wiles A.J. and J.K. Narcisse (1971). Am. Ind. Hyg. Assoc. J. 32:539-545.

ANNEX 1 TO SIDS 127195 DMAC
PROCESS FLOW SHEET