Documentation of the 3M Exposure Guideline for

N-Methylperfluorobutanesulfonamidoethanol (N-MeFBSE)

3M EG: 1.0 mg/m^3 (0.07 ppm), 8-hour TWA

Date: January 3, 2006

SUBSTANCE IDENTIFICATION

Chemical Name:	1-Butanesulfonamide,1,1,2,2,3,3,4,4,4-nonafluoro-N-(2-hydroxyethyl)-N-methyl-
Synonyms:	N-MeFBSE; C4 Ethanol; F-9260; T-7599
CAS Number:	34454-97-2
Molecular Formula:	$C_7H_8F_9NO_3S$
Structural Formula:	$CF_3CF_2CF_2CF_2SO_2N(CH_3)CH_2CH_2OH$
3M MSDS Number:	09-0610-7
Manufacturer:	3M SMD AC & ANTWERP

USE AND EXPOSURE DATA

Primary uses: N-MeFBSE is primarily an isolated intermediate in the synthesis of various perfluorinated C4 sulfonyl compounds (*e.g.*, C4 acrylate) at 3M Decatur.

Production Locations: N-MEFBSE is produced at 3M Decatur and 3M Zwijndrecht (Antwerp).

Exposure Levels: Exposures are task-dependent with the highest exposures occurring during draining of molten N-MeFBSE into drums.

PHYSICOCHEMICAL PROPERTIES [1]

Physical State:	Waxy solid, flakes
Molecular Weight:	357.2
Melting Point:	149 °F (65 °C)
Boiling Point:	257 °C
Vapor Pressure:	0.0000298 mm Hg @ 20 °C (measured) 0.0106 mm Hg @ 55 °C (measured)
Vapor Density:	>1
Odor description and Threshold:	No data available
Flash Point:	Not combustible
Solubility in Water:	Nil
pH:	Not applicable
Log P (octanol:water):	3.4 (calculated)
Stability:	Highly stable
Conversion:	1 mg/m^3 = 0.07 ppm

SAMPLING AND ANALYTICAL METHODS: Air samples can be collected (up to 1 liter per minute sampling rate) using OSHA Versatile Sampler (OVS) tubes with glass fiber filters and 180/60 mg of XAD-4 resin. Analysis is by LCMS (ETS Method 8-65.0) with a lower limit of quantitation at approximately 0.32 μg.

CHEMICAL INFORMATION: N-MeFBSE is a relatively nonvolatile at room temperature, but has a significant vapor pressure in the molten state.

ACUTE TOXCITY DATA

Oral:	LD_{50} > 2000 mg/kg. N-MeFBSE was administered by oral gavage to three male and three female Wistar rats at 2000 mg/kg body weight. No mortality occurred. Lethargy, uncoordinated movements, hunched posture and/or chromodacryorrhoea were noted among the females between days 1 and 3. Lethargy and uncoodrinated movements were noted among the males between days 1 and 2. The mean body weight gain shown by the animals

over the study period was considered to be normal. No abnormalities were found at macroscopic post mortem examination of the animals. [2]

Dermal Irritation: Not a dermal irritant. Three rabbits were exposed to 0.5 grams of N-MeFBSE, applied onto clipped skin for 4 hours using a semi-occlusive dressing. Observations were made, 1, 24, 48 and 72 hours after exposure. Exposure to N-MeFBSE did not result in any skin irritation. [3]

Eye Irritation: Not a significant ocular irritant. Single samples of approximately 62 mg of N-MeFBSE (a volume of approximately 0.1 ml) were instilled into one eye of each of three rabbits. Observations were made 1, 24, 48 and 72 hours and 7 days after instillation. Instillation of the test substance resulted in effects on the iris and conjunctivae. Iridial irritation (grade 1) was observed in two animals and had resolved within 24 hours. Irritation of the conjunctivae was seen as redness, chemosis and discharge, which had completely resolved within 7 days in all animals. Remnants of the test substance were present in the eyes of all animals on day 1. [4]

SENSITIZATION

Dermal Sensitization: Not a dermal sensitizer. Ten female albino guinea pigs (Dunkin Hartley strain) were intradermally injected with a 5% concentration of N-MeFBSE and epidermally exposed to a 20% concentration [guinea pig maximization test]. Five control female animals were similarly treated, but with vehicle alone (polyethylene glycol 400). Approximately 24 hours before the epidermal induction exposure all animals were treated with 10% SDS. Two weeks after the epidermal application all animals were challenged with a 20% test substance concentration and the vehicle. No evidence of an allergic skin reaction was noted in either the experimental or control animals after the challenge exposure. [5]

GENOTOXICITY

Mutagenicity: Negative both with and without S9-mix (5% v/v) in *Salmonella typhimurium* (strains TA1535, TA1537, TA100 and TA98) and negative both with and without S9-mix (10% v/v) in *Escherichia coli* (Wp2uvrA) reverse mutation assays. [6]

Chromosomal aberration:

N-MeFBSE did not induce a statistically significant or biologically relevant increase in the number of cells (cultured peripheral human lymphocytes) with

chromosome aberrations in the absence and in the presence of S9-mix, in two independently repeated experiments. It is concluded that this test is valid and that N-MeFBSE is not clastogenic in human lymphocytes under the experimental conditions described in this report. [7]

PHARMACOKINETICS:

Serum and Liver $T_{1/2}$

The apparent serum and liver half-life of elimination ($T_{1/2}$) for N-MeFBSE was estimated in male Sprague-Dawley rats (n = 9 rats; 3/exposure period). [8] The rats received a single 30 mg/kg dose of N-MeFBSE in propylene glycol by oral gavage at a volume of 5 mL/kg body weight. The vehicle control group rats (n = 6) received a single dose of propylene glycol at a volume of 5 mL/kg. Necropsies were performed at 4 hours (day zero), 28 hours (day one), and 100 hours (day four) post dose. At necropsy, there were no significant differences in body weight or gross macroscopic observations between the treatment group and the control group. The concentration of N-MeFBSE, in serum and liver was monitored by the nonspecific method of total organic fluorine (TOF) analysis, which measures the amount of the parent compound plus any metabolites in these tissues. A limited number of sample collections were taken in this study, therefore, the apparent elimination $T_{1/2}$ and the maximum tissue concentrations of TOF are best estimates based on the available data. The rates of elimination of N-MeFBSE were similar in both serum and liver. The apparent serum and liver $T_{1/2}$ for N-MeFBSE was approximately 17 hours.

REPEAT-DOSE TOXICITY DATA

Repeated Dose 28-Day Oral Toxicity Study in Rodents (OECD No. 407) [9]

A group of 14 male and 14 female SPF-bred Sprague Dawley rats received N-MeFBSE orally at a dose of 30 mg/kg/day for 28 days. On day 29, 8/sex were necropsied and the remaining 6/sex animals entered a recovery period (no treatment). Three/sex were necropsied after two weeks of recovery and the remaining 3/sex after four weeks of recovery. A similar group of 14/sex control rats was orally dosed with vehicle (1% aqueous carboxymethyl cellulose). The following parameters were evaluated: clinical signs (twice daily during treatment or once daily during recovery), body weight (twice weekly), food consumption (weekly), clinical pathology (after 4 weeks and at the end of recovery period), gross pathology (at termination), and organ weights and histopathology on a selection of tissues (*e.g.* adrenals, kidneys, liver, lymph nodes, ovaries, pancreas, spleen, testis, and thymus).

The following were noted in this study:

- No mortality;
- Hunched posture was incidentally noted in two females during the first week of recovery;
- No changes in body weight or body weight gain during both treatment and recovery periods;
- No changes in absolute or relative food consumption during both treatment and recovery periods;
- No macroscopic pathology noted;
- No toxicologically relevant changes in organ weights [any finds were absent in the opposite sex and did not occur during treatment];
- Hemolytic serum samples noted: 1) after 4 weeks of treatment in 4/14 males and 3/14 females; 2) after two weeks of recovery in all males; and 3) after 4 weeks of recovery still in 1/3 males; and
- After 4 weeks of treatment, a slight increase (microscopically observed) in severity of hematopoiesis (primarily erythropoiesis) in the spleen of males [decreased after 4 weeks of recovery].

Apart from a slightly increased severity of splenic hematopoiesis in male rats (which tended to decrease during the recovery phase), treatment for 28 days with N-MeFBSE did not result in any observed systemic toxicity or organ dysfunction (either at the macroscopic or microscopic level). The NOAEL for this study was determined to be 30 mg/kg/day.

Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD No. 422) [10]

Sixty male and sixty female Crl:CD(SD)IGS VAF/Plus rats were assigned to four dosage groups with 15 rats per sex per group. The test substance (N-MeFBSE) or vehicle (carboxymethylcellulose) was orally (gavage) administered to the male rats beginning 14 days before cohabitation and continuing until sacrifice, after completion of the cohabitation period, after a minimum of 28 days of dosage, and to the female rats beginning 14 days before cohabitation and continuing until day 5 of lactation (DL5). Dosages were 0 (vehicle), 10, 50, and 250 mg/kg/day.

Five males and five females from each dose group were assigned to a functional observational battery (FOB) and motor activity assessment. Five males and five females from each dose group were assigned to hematology and clinical biochemistry evaluations. Histological evaluations were performed on the last ten rats per sex in each dose group. Rats were observed for viability at least twice daily; observations for clinical signs of effects of the test substance, abortions, premature deliveries and deaths were made daily before dosing. Other observations/measurements included: pup weights, clinical observations, body weights, feed consumption, estrus cycle evaluation, motor activity, organ weights (e.g. liver, kidneys, adrenals, thymus, spleen, heart, ovaries, uterus), gross lesions and histopathological lesions. On DL5, pups were sacrificed and examined for gross lesions; pups found dead were also examined for gross lesions.

The following changes were noted:

Males at 10 mg N-MeFBSE/kg body weight-day:

- No treatment-related findings in any animal; and
- All animals survived to scheduled sacrifice.

Males at 50 mg N-MeFBSE/kg body weight-day:

- All animals survived to scheduled sacrifice;
- Body weight gains significantly decreased on study days 1 to 36;
- Absolute and relative feed consumption values were significantly reduced on study days 1- 8;
- Absolute weights of the kidneys were significantly increased;
- The ratios of the weights of the kidneys and liver to terminal body weight were significantly increased;
- No treatment-related effects on any hematology or clinical chemistry value;
- No treatment-related effects on any mating or fertility parameter;
- Treatment-related microscopic changes (minimal or mild enlargement of centrilobular hepatocytes) in the livers of 4/10 male rats [the enlargement was due to an increased amount of finely granular, dense eosinophilic cytoplasm];
- No significant differences in any clinical observations or necropsy observations;
- No statistically or biologically important differences in the measures of the FOB; and
- No statistically or biologically important differences in the measures of motor activity.

Males at 250 mg N-MeFBSE/kg body weight-day:

- All animals survived to scheduled sacrifice;
- Significant increases in salivation, perioral substance and urine-stained abdominal fur;
- Body weight gains significantly decreased on study days 1 to 36;
- Body weights were significantly reduced on study days 29 and 36;
- Absolute and relative feed consumption values were significantly reduced on study days 1- 15 and 1 - 36;
- Terminal body weights were significantly reduced;
- Absolute weights of the kidneys were significantly increased;
- Absolute liver weight was significantly increased;
- The ratios of the weights of the kidneys and liver to terminal body weight were significantly increased;
- No treatment-related effects on any hematology or clinical chemistry value;
- No treatment-related effects on any mating or fertility parameter;
- Treatment-related microscopic changes (minimal or mild enlargement of centrilobular hepatocytes) in the livers of most of male rats [the enlargement was due to an increased amount of finely granular, dense eosinophilic cytoplasm];
- Three of the male rats also had necrosis of individual enlarged centrilobular hepatocytes;
- Treatment-related microscopic changes in the stomach of two rats (focal erosion of the pyloric glandular mucosa);
- No significant differences in any clinical observations or necropsy observations;
- No statistically or biologically important differences in the measures of the FOB; and
- No statistically or biologically important differences in the measures of motor activity.

Females at 10 mg N-MeFBSE/kg body weight-day:

- All animals survived to scheduled sacrifice; and
- No treatment-related findings in any animal.

Females at 50 mg N-MeFBSE/kg body weight-day:

- All animals survived to scheduled sacrifice; and
- No treatment-related findings in any animal.

Females at 250 mg N-MeFBSE/kg body weight-day:

- All animals survived to scheduled sacrifice;
- No significant differences in any clinical observations or necropsy observations;
- Body weight gains significantly reduced during precohabitation on study days 1-8 and 1-15;
- Terminal body weights reduced;
- Absolute liver weights significantly increased;
- Ratio of the liver to brain weight significantly increased;
- Treatment-related microscopic findings in the liver and thymus;
- No treatment-related effects on any hematology or clinical chemistry value;
- No changes in absolute or relative feed consumption;
- All estrus, mating and fertility parameters were unaffected by treatment;

- No statistically or biologically important differences in the measures of the FOB;
- No statistically or biologically important differences in the measures of motor activity;

Reproductive/Developmental Parameters

- The number of live born pups was significantly reduced;
- The number of stillborn pups was significantly increased;
- The number of pups found dead or presumed cannibalized on day 1 and days 2-5 postpartum was significantly increased;
- The viability index and number of pups surviving per litter on postpartum day 5 were significantly reduced;
- Pup body weights per litter were reduced on postpartum days 1 and 5;
- Values for the number of dams delivering litters, duration of gestation, averages for implantation sites per delivered litter, gestation index, number of dams with stillborn pups, dams with all pups dying stillborn pups, surviving pups per litter on postpartum day 1 and pup sex ratios were unaffected;
- No clinical or necropsy observations of the F1 pups were attributable to treatment.

On the basis of these data, the following were determined[1]:

- The paternal no-observable-adverse-effect-level (NOAEL) for N-MeFBSE is 10 mg/kg/day (the 50 mg/kg/day caused reduced weight gain during precohabitation, reduced absolute and relative feed consumptions, increased absolute and relative liver and kidney weight, and liver histopathology);

- The maternal NOAEL is 50 mg/kg/day (the 250 mg/kg/day dosage caused reduced weight gain during precohabitation, reduced terminal body weights, increased absolute and relative liver weight, and histopathology of the liver and thymus);

- The reproductive NOAEL is greater than 250 mg/kg/day (all estrous, mating, and fertility parameters were unaffected by dosages of the test substance as high as 250 mg/kg/day); and

- The NOAEL for viability and growth in the offspring is 50 mg/kg/day (dosages of 250 mg/kg/day caused potential mortality and decreased pup body weights).

[1] At the request of the 3M EG Committee, the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD No. 422) Final Report and its conclusions were peer-reviewed by two outside independent consultants (Dr. Jack Moore and Dr. John DeSesso). Both consultants agreed with the conclusions of the report, including the NOAELs.

3M EXPOSURE GUIDELINE (EG) RATIONALE

EXPOSURE GUIDELINE: The 3M Exposure Guideline (EG) for N-MeFBSE of 1 mg/m^3 (0.07 ppm), 8-hour TWA is recommended.

RATIONALE: Five sub-uncertainty factors were used by the EG Committee to establish a total uncertainty factor which was used in the derivation of the 3M EG. The sub-uncertainty factors, their numerical values, as well as a brief comment regarding the Committee's rationale for each UF are given in the following table:

SUB-FACTOR	RATIONALE	UF VALUE
Extrapolation to NOAEL	The paternal NOAEL of 10 mg/kg-day from the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD No. 422) was used.	1
Animal to Human Extrapolation	To account for uncertainty in extrapolating results observed in rats to humans the Committee decided to apply a standard cross-species scaling factor.	6
Duration of Exposure	While uncertainty still exists, the results of the repeat dose toxicity studies were considered by the Committee to be adequate to understand the biological response of N-MeFBSE for purposes of establishing an exposure guideline.	3
Dose – Response	The Committee felt that the available data from the two repeat-dose studies (OECD 407and 422) for N-MeFBSE provided good understanding of the dose-response relationship.	2
Severity of Response	Microscopic changes (minimal or mild enlargement of centrilobular hepatocytes) in the livers of 4/10 male rats at the 50 mg/kg-day were observed. These are not considered to be very serious responses; however repeat-dose studies greater than 28 days are not available and, therefore, some uncertainty still exists.	2

Based on the values for the five sub-uncertainty values, the total safety factor derived by Committee consensus is 72. Assuming a 70 kg body weight and 10 m^3 per workday inhalation volume, an EG of 1 mg/m^3 (rounded from 0.97 mg/m^3) is obtained.

REFERENCES

[1] 3M Company. (3M ID: 09-0610-7) Material Safety Data Sheet for N-MeFBSE Alcohol F-9260.

[2] NOTOX. (January 2002). Acute Oral Toxicity (NOTOX Project 332077, NOTOX Substance 113742).

[3] NOTOX. (January 2002). Acute Toxicity –Skin Irritation (NOTOX Project 332088; NOTOX Substance 113742).

[4] NOTOX. (January 2002). Acute Eye Irritation (NOTOX Project 332099, NOTOX Substance 113742.

[5] NOTOX. (February 2002). Dermal Sensitization (NOTOX Project 332101, NOTOX Substance 113742).

[6] NOTOX. (March 2002). Mutagenicity Assay (NOTOX Project 332 112, NOTOX Substance 113742).

[7] NOTOX. (June 2002). Chromosomal Aberration (NOTOX Project 342416, NOTOX Substance 113742).

[8] 3M Medical Department, Corporate Toxicology Strategic Toxicology Laboratory. (5/23/2002). Pharmacokinetic Study of N-methyl perfluorobutylsulfonamido ethyl alcohol (N-MeFBSE alcohol, T-7599.8), N-methyl perfluorobutylsulfonamide (N-MeFBSA amide, T-7601.7), N-methyl perfluorobutylsulfonamido ethyl acrylate (N-MeFBSEA acrylate, T-7600.6), and Perfluorobutanesulfonate potassium salt (PFBS) or C4 sulfonate, T-7485.16) in Rats. Strategic Toxicology Laboratory Study Number 75.

[9] NOTOX. (March 2000). Exploratory 28-day Oral Toxicity Study. NOTOX Safety & Environmental Research B.V. 3M Study Number: T-7250.

[10] NOTOX (February 2004), Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test with N-MeFBSE Administered by Oral Gavage in Wistar Rats. (NOTOX Project 385717, NOTOX Substance 113742)

Appendix

3M EG Calculation for N-MeFBSE using the Uncertainty/Safety Factor Methodology:

$$\mathrm{EG}\left(\mathrm{mg/m^3}\right) = \frac{(\mathrm{NOAEL})(\mathrm{Body\ weight})}{(\mathrm{Volume\ of\ air\ breathed/8\text{-}hr\ work\ day})(\mathrm{UF})}$$

NOAEL = 10 mg/kg-day

Body Weight = 70 kg

Volume of air breathed/working day = 10 m^3

UF = Total Uncertainty Factor = 72 [made up from the following sub-factors]:

Extrapolation to NOAEL = 1

Extrapolation from Experimental Animals to Humans = 6

Extrapolation for Duration of Exposure = 3

Dose-Response for Critical Effect = 2

Severity (Significance) of Critical Effect = 2

APPROVALS

Documentation of the 3M Exposure Guideline (EG) for

N-Methylperfluorobutanesulfonamidoethanol (N-MeFBSE)

3M EG: 1.0 mg/m^3 (0.07 ppm), 8-hour TWA

Effective Date: 1-3-2006

Chairperson, 3M EG Committee
3M Medical Department — Date: 12-2-2005

Director, Corporate Toxicology &
Regulatory Services
3M Medical Department — Date: 12-6-2005

Manager, Corporate Industrial Hygiene
3M Environmental, Health & Safety Operations — Date: 12-8-2005

Director, Medical Services
3M Medical Department — Date: 12/17/05

Staff Vice President and Medical Director
3M Medical Department — Date: 1/3/06