

FYI

FYI - 0696 - 1275

**elf atochem**



**Elf Atochem North America, Inc.**

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Philadelphia, PA 19103-3222  
Tel: 215.419.7000

ORIGINAL



FYI-96-001275

June 14, 1996

UPS NEXT DAY DELIVERY



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Document Control Office (7407)  
Office of Pollution Prevention and Toxics  
Environmental Protection Agency  
401 M St., S.W.  
Washington, D.C. 20460

Confidential

Subject: TSCA FYI Coordinator

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96 JUN 18 PM 3:05  
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Dear Sir/Madam:

Elf Atochem North America Inc. is submitting the enclosed study to the Environmental Protection Agency (EPA) on a "For Your Information (FYI)" basis. This study does not involve effects in humans.

The enclosed study recently came into our possession and provides information on isoamyl bromide (CAS Number 107-82-4). The title of the study is *Acute Oral Toxicity in Rats*. The following is a summary of the adverse effects observed in the study:

Isoamyl bromide was tested to determine the acute oral toxicity. No deaths occurred when 2000 mg/kg was administered to the rat. Sedation and ptosis were noted 30 minutes after administration; sedation was also noted at 24 hours. No clinical signs were apparent from the 48 hour observation until the end of the study (14 days). Although nervous system effects are known for other bromides, we were unable to find any previous studies for isoamyl bromide in the literature.

Nothing in this letter or the enclosed study report is considered confidential business information of Elf Atochem.

TSCA FYI Submission  
Isoamyl Bromide  
June 14, 1996  
Page 2

Elf Atochem North America, Inc. does not currently manufacture or market isoamyl bromide.

Further questions regarding this submission may be directed to me at (215) 419-5890.

Sincerely,

A handwritten signature in cursive script that reads "Debra Randall".

Debra Randall, D.A.B.T.  
Product Safety Manager

**SPONSOR**

Elf Atochem S.A.  
La Défense 10 - Cédex 42  
92091 Paris-la-Défense  
France

**STUDY TITLE**

ACUTE ORAL TOXICITY  
IN RATS

**TEST SUBSTANCE**

Iso-AMYL BROMIDE

**STUDY DIRECTOR**

Stéphane de Jouffrey

**STUDY COMPLETION DATE**

19 April 1996

**PERFORMING LABORATORY**

Centre International de Toxicologie (C.I.T.)  
Miserey - 27005 Evreux - France

**LABORATORY STUDY NUMBER**

13724 TAR

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**STATEMENT OF THE STUDY DIRECTOR**

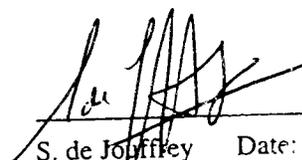
The study was performed in compliance with the following principles of Good Laboratory Practice Regulations:

- . O.E.C.D. principles of Good Laboratory Practice, C(81)30(final) Annex 2, May 12, 1981,
- . Décret N° 90-206 du 7 mars 1990 concernant les Bonnes Pratiques de Laboratoire (Ministère de l'Industrie et de l'Aménagement du Territoire).

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained during the performance of the study.

This study was performed at the Centre International de Toxicologie (C.I.T.), Miserey, 27005 Evreux, France.

Toxicology

  
S. de Joffrey Date: 19 April 1996  
Study Director  
Doctor of Veterinary Medicine  
Head of Short-term and Environmental  
Toxicology

**OTHER SCIENTISTS INVOLVED IN THIS STUDY**

For Pharmacy: J. Richard  
Doctor of Pharmacy

For Toxicology: C. Pelcot  
Study Supervisor

**STATEMENT OF QUALITY ASSURANCE UNIT****1. Specific study inspections**

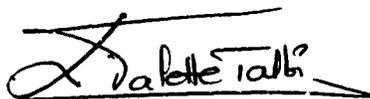
Type of inspections	Dates (day/month/year)		
	Inspections	Report to Study Director (*)	Report to Management (*)
Protocol	6 Dec. 95	28 Dec. 95	28 Dec. 95
Report	29 Mar. 96	1 Apr. 96	2 Apr. 96

**2. Routine inspections performed on other studies of the same type according to a frequency defined in Q.A.U. procedures**

Inspected phase	Dates (day/month/year)		
	Inspections	Report to Study Director (*)	Report to Management (*)
Test substance/preparation	17 Oct. 95	18 Oct. 95	18 Oct. 95
Treatment/test substance	14 Nov. 95	20 Nov. 95	20 Nov. 95

The inspections were performed in compliance with C.I.T. Quality Assurance Unit procedures and the Good Laboratory Practice Regulations.

(\*) The dates mentioned correspond to the dates of signature of audit reports by Study Director and Management.



L. Valette-Talbi D. Sc. April 1996  
 Doctor of Biochemistry  
 Head of Quality Assurance Unit  
 and Scientific Archives

## SUMMARY

At the request of Elf Atochem S.A., Paris-la-Défense, France, the acute oral toxicity of the test substance Iso-AMYL BROMIDE was evaluated in rats according to O.E.C.D. (No. 401, 24th February 1987) and E.C. (92/69/E.E.C., B<sub>1</sub>) guidelines. The study was conducted in compliance with the principles of Good Laboratory Practice Regulations.

## Methods

The test substance was administered by oral route to one group of ten fasted Sprague-Dawley rats (five males and five females).

The test substance was administered in its original form, by gavage, at a dose of 2000 mg/kg, taking into consideration that the density of the test substance was 1.21.

Clinical signs, mortality and body weight gain were checked for a period of 14 days following the single administration of the test substance.

All animals were subjected to necropsy.

## Results

Sedation or hypoactivity, piloerection and ptosis were observed in all animals 30 minutes after treatment. Ptosis was still present 4 hours after treatment; sedation and piloerection were noted until day 2 in all animals.

No clinical signs persisted on day 3.

No death occurred at 2000 mg/kg.

Body weight gain of the animals was not influenced by treatment.

The necropsy of the animals at the end of the study revealed no apparent abnormalities.

## Conclusion

Under our experimental conditions, the oral LD<sub>50</sub> of the test substance Iso-AMYL BROMIDE was higher than or equal to 2000 mg/kg in rats.

## 1. INTRODUCTION

The objective of this study was to evaluate the toxicity of the test substance Iso-AMYL BROMIDE following a single oral administration in rats.

In the assessment of the toxic characteristics of a test substance, determination of acute oral toxicity is an initial step. It provides information on health hazards likely to arise from a short-term exposure by the oral route in Man.

The study was conducted in compliance with:

- . O.E.C.D. guideline No. 401, 24th February 1987,
- . E.C. Directive No. 92/69/E.E.C., B<sub>1</sub>, 31st July 1992.

## 2. MATERIALS AND METHODS

### 2.1. TEST SUBSTANCE

#### 2.1.1 Identification

The test substance Iso-AMYL BROMIDE used in the study was supplied by Elf Atochem S.A.

Documentation supplied by the Sponsor identified the test substance as follows:

- . name:
  - protocol and labelling: Iso-AMYL BROMIDE
- . batch number:
  - protocol: 4-153-1
  - labelling: 4-153-1 CAL 6779/95
- . description: colourless liquid
- . quantity and container: 150 g in one glass flask
- . date of receipt: 19.12.95
- . storage conditions: at room temperature and protected from light.
- . purity: 99.1%.

Data relating to the characterization of the test substance are documented in a test article description and an analytical certificate (presented in appendix 1) provided by the Sponsor.

#### 2.1.2 Preparation

The test substance was administered in its original form.

## 2.2. TEST SYSTEM

### 2.2.1 Animals

Species, strain: rat, Sprague-Dawley ICO: CFA-SD (IOPS Caw).

Reason for this choice: rodent species commonly requested by the international regulations for this type of study.

Breeder: Iffa Crédo, 69210 L'Arbresle, France.

Number and sex: one group of ten animals (five males and five females).

Age/weight: on the day of treatment, the animals were approximately six weeks old, and had a mean body weight  $\pm$  standard deviation of  $192 \pm 9$  g for the males and  $152 \pm 8$  g for the females.

Acclimatization: at least five days before the beginning of the study.

Identification of the animals: the animals were identified individually by earmarks or earnotches.

### 2.2.2 Environmental conditions

During the acclimatization period and during the main test, the conditions in the animal room were as follows:

. temperature:  $21 \pm 2^\circ\text{C}$

. relative humidity: 30 to 70%

. light/dark cycle: 12 h/12 h

. ventilation: about 12 cycles/hour of filtered, non-recycled air.

The temperature and relative humidity were recorded continuously and records retained.

The housing conditions (temperature, relative humidity and ventilation) were checked monthly.

The animals were housed in polycarbonate cages (48 cm x 27 cm x 20 cm). Each cage contained four to seven animals of the same sex during the acclimatization period and five rats of the same sex during the treatment period. Each cage contained dust-free sawdust (SICSA, 94142 Alfortville, France).

Bacteriological analysis of the sawdust and detection of possible contaminants (pesticides, heavy metals) are performed periodically.

### 2.2.3 Food and water

All the animals had free access to AO4 C pelleted diet (U.A.R., 91360 Villemoisson-sur-Orge, France), except as noted in "2.3.1 Fasting of the animals".

Each batch of food was analysed (composition and contaminants) by the supplier.

The diet formula is presented in appendix 2.

Drinking water filtered by a F.G. Millipore membrane (0.22 micron) was provided *ad libitum*.

Bacteriological and chemical analysis of the water and diet and detection of possible contaminants (pesticides, heavy metals and nitrosamines) are performed periodically.

Results are archived at C.I.T.

It was verified that no contaminants in the diet or water at levels likely to influence the outcome of the study were present.

### 2.3. TREATMENT

As the test substance was anticipated to be non-toxic at 2000 mg/kg, a limit test was performed by administering 2000 mg/kg of the test substance to one group of ten animals (five males and five females).

#### 2.3.1 Fasting of the animals

The animals were fasted for an overnight period of approximately 18 hours before dosing, but had free access to water. Food was given approximately 4 hours after administration of the test substance.

#### 2.3.2 Administration of the test substance

The test substance was administered in its original form taking into consideration that its density was 1.21.

The administration was performed in a single dose by oral route using a stainless steel round tipped probe (diameter: 18 G.2", Perfektum: Poffert & Sons Inc., New Hyde Park, New York 11040, U.S.A.) fitted to a 1 ml glass syringe (0.01 ml graduations, Record: Carriert. 15005 Paris, France).

The volume administered to each animal was adjusted according to body weight determined on the day of treatment.

#### 2.3.3 Date of treatment and duration of the study

The single administration was performed on 4.1.96 in the morning (day 1) and was followed by a 14-day observation period until 18.1.96 (day 15).

### 2.4. CLINICAL EXAMINATIONS

The single administration was performed in the morning of day 1; it was followed by a 14-day observation period until day 15.

#### 2.4.1 Clinical signs and mortality

The animals were observed frequently during the hours following administration of the test substance, for detection of possible treatment-related clinical signs. Thereafter, observation of the animals was made at least once a day. Type, time of onset and duration of clinical signs were recorded for each animal individually.

Time of death was recorded individually, in terms of the number of hours or days after dosing.

#### 2.4.2 Body weight

The animals were weighed individually just before administration of the test substance on day 1 and then on days 8 and 15.

The body weight gain of the treated animals was compared to a reference curve of C.I.T. control animals with the same initial body weight.

## 2.5. NECROPSY

On day 15, all animals were killed by CO<sub>2</sub> inhalation in excess and a macroscopic examination was performed.

After opening the thoracic and abdominal cavities, a macroscopic examination of the main organs (digestive tract, heart, kidneys, liver, lungs, pancreas, spleen and any other organs with obvious abnormalities) was performed.

In case of macroscopic lesions, organ samples were taken and preserved in 10% buffered formalin.

No microscopic examination was performed.

## 2.6. DATA EVALUATION

Evaluation of the toxicity of the test substance following a single oral administration in rats should include the relationship, if any, between the animals' exposure to the test substance and the incidence and severity of all abnormalities including behavioural and clinical abnormalities, macroscopic lesions, body weight changes, mortality and any other toxic effects.

Following Commission Directive 93/21/E.E.C., the classification of the test substance is based on the criteria presented below:

LD <sub>50</sub> oral route (mg/kg)	Labelling sentence	Indication of danger	Symbol
≤ 25	R28 Very toxic if swallowed	Very toxic	T <sup>+</sup>
25 < and ≤ 200	R25 Toxic if swallowed	Toxic	T
200 < and ≤ 2000	R22 Harmful if swallowed	Harmful	X <sub>n</sub>
> 2000	None	None	None

## 2.7. ARCHIVES

The study documentation and materials, namely:

- . protocol and possible amendments,
- . raw data,
- . correspondence,
- . final report and possible amendments,

are stored in the archives of C.I.T., Miserey, 27005 Evreux, France, for five years after the end of the *in vivo* phase of the study. At the end of this period, the study documentation will be returned to the Sponsor.

0 0 1 3

### 3. RESULTS

#### 3.1. CLINICAL EXAMINATIONS

##### 3.1.1 Clinical signs (table 1)

Sedation or hypoactivity, piloerection and ptosis were observed in all animals 30 minutes after treatment. Ptosis was still present 4 hours after treatment; sedation and piloerection were noted until day 2 in all animals.

No clinical signs persisted on day 3.

##### 3.1.2 Mortality (table 1)

No death occurred.

##### 3.1.3 Body weight (treated animals: figure 1, table 2) (historical control animals: figure 2, table 3)

Body weight gain of treated animals was not influenced by treatment.

#### 3.2. PATHOLOGY (table 4)

Macroscopic examination of the main organs of the animals revealed no apparent abnormalities.

### 4. CONCLUSION

Under our experimental conditions, the oral LD<sub>0</sub> of the test substance Iso-AMYL BROMIDE was higher than or equal to 2000 mg/kg in rats.

Figure 1: Body weight of treated rats (g)

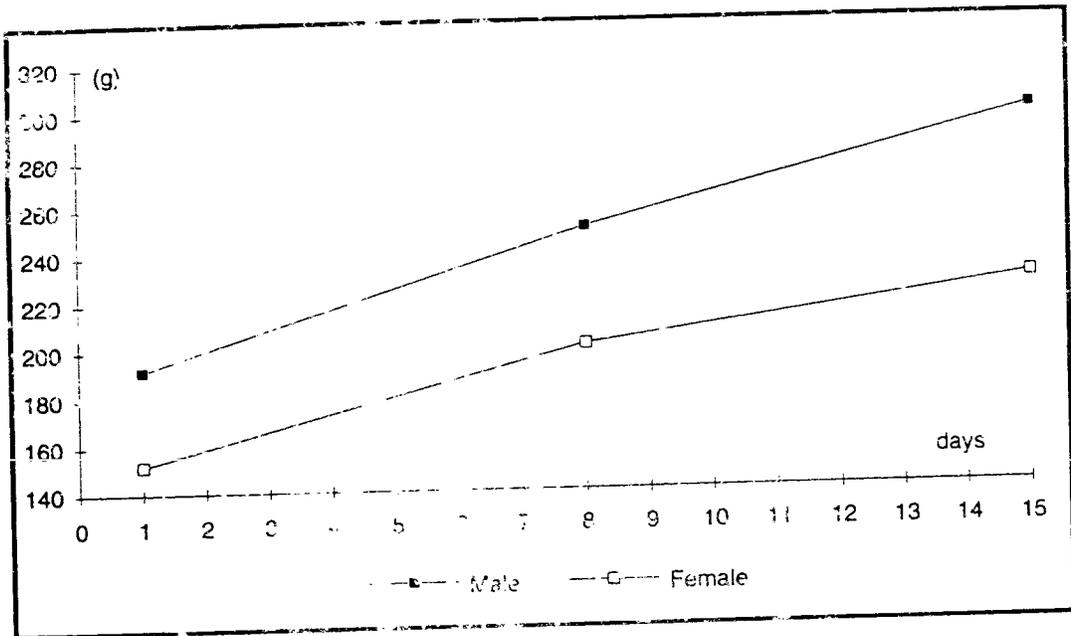
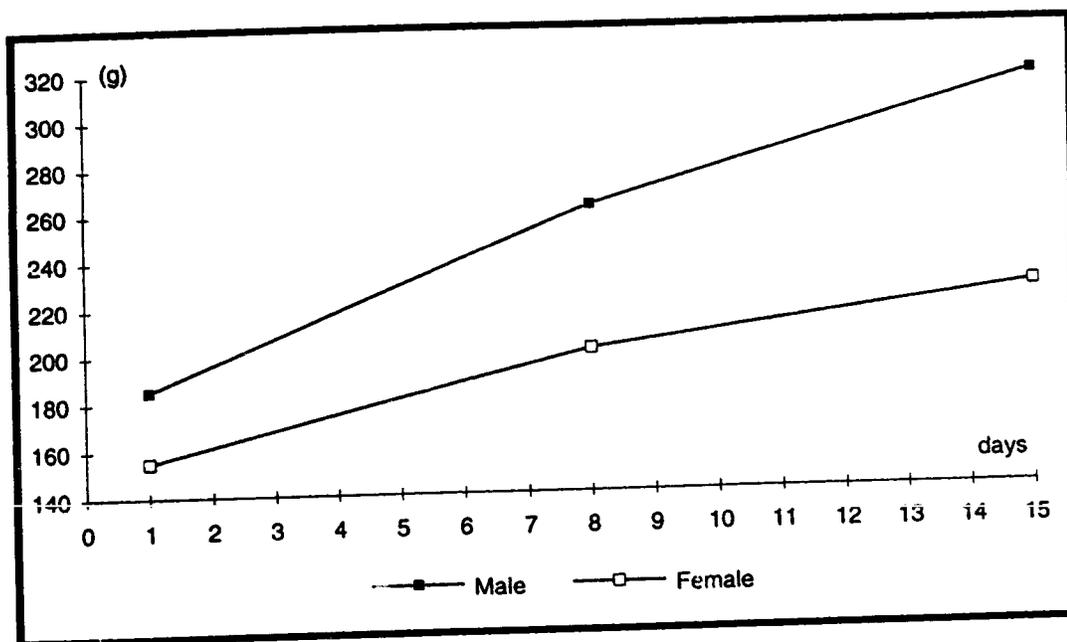


Figure 2: Body weight of C.I.T. historical control rats (g)



e.g.: C.I.T. Historical data of animals dosed by the oral route: results of control animals from October 1990 to January 1996.

Table 1: Individual clinical signs and mortality

Dose (mg/kg)	Time	Animals		Mortality	Clinical signs
		Males	Females		
2000	30 min	01-02-03-04-05	01-03-04-05	No	Sedation, piloerection, ptosis
			02	No	Piloerection, hypoactivity
	1-2-4 h	01-02-03-04-05	01-02-03-04-05	No	Sedation, piloerection, ptosis
	D 2	01-02-03-04-05	01-02-03-04-05	No	Sedation, piloerection
	D 3 to D 15	01-02-03-04-05	01-02-03-04-05	No	None

min: minutes

h : hour

D : day

Table 2: Individual and mean body weight and weekly body weight change of treated rats (g)

Dose mg/kg	Volume ml/kg	Sex	Animals	Days				
				1	(1)	8	(1)	15
2000	1.66	Male	01	184	60	244	3	247
			02	183	53	236	58	294
			03	188	66	254	75	329
			04	202	56	258	65	323
			05	201	60	261	39	300
			M	192	59	251	48	299
			SD	9	5	10	28	32
2000	1.66	Female	01	154	54	208	35	243
			02	146	47	193	26	219
			03	152	41	193	19	212
			04	143	40	183	33	216
			05	164	64	228	20	248
			M	152	49	207	27	228
			SD	8	10	18	7	17

(1) = Body weight gain  
M = Mean  
SD = Standard Deviation

Table 3: Mean body weight and weekly body weight change of C.I.T. historical control rats (g)

**BODY WEIGHT OF CONTROL RATS**

(g)

Dose mg/kg	Volume ml/kg	Sex		Days		
				1	8	15
0	10	Male	M	185	262	317
			SD	8	13	20
			n	90	90	90
0	10	Female	M	155	201	225
			SD	9	15	19
			n	90	90	90

M : mean

SD: standard deviation

n : number of animals

**BODY WEIGHT CHANGE OF CONTROL RATS**

(g)

Dose mg/kg	Volume ml/kg	Sex		Days	
				1 to 8	8 to 15
0	10	Male	M	77	55
			SD	9	13
0	10	Female	M	46	25
			SD	10	11

M : mean

SD: standard deviation

e.g.: C.I.T. Historical data of animals dosed by the oral route: results of control animals from October 1990 to January 1996.

Table 4: Individual macroscopic examinations at necropsy

Dose mg/kg	Time	Animals		Macroscopic abnormalities
		Males	Females	
2000	D 15	01-02-03-04-05	01-02-03-04-05	None

D : day

APPENDICES

1. Test article description and analytical certificate

## TOXICOLOGY DEPARTMENT

CONFIDENTIAL

21 November 1995

elf atochem s.a.

La défense 10, cedex 42  
92091 Paris-la-Défense, France

## TEST ARTICLE DESCRIPTION

Iso-AMYL BROMIDE

## STRUCTURAL FORMULA

 $\text{BrCH}_2\text{-CH}_2\text{-CH(CH}_3\text{)-CH}_3$ 

## IDENTITY

Test article name : Iso-Amyl bromide  
Chemical name : Bromo-1-methyl-3-butane  
CAS number : 107-82-4  
Molecular formula :  $\text{BrC}_5\text{H}_{11}$   
Molecular weight : 151  
Purity : 99.1%  
Origin and batch : Elf Atochem, Port-de-Bouc  
Batch : 4-153-1  
Elf Atochem filing number : CAL 6779/95

## PHYSICAL AND CHEMICAL PROPERTIES

Appearance : Colorless liquid  
Specific gravity : 1.26  
Melting point :  $-112^\circ\text{C}$   
Boiling point :  $121^\circ\text{C}$   
Vapor pressure : 25 mbar at  $20^\circ\text{C}$   
Flash point :  $32^\circ\text{C}$  (closed cup)  
Solubility : < 0.1% in water  
: soluble in DMSO  
: soluble in ethylic alcohol

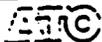
## TOXICOLOGICAL INFORMATIONS AND USE SAFETY

See MSDS.

## STORAGE AND DISPOSAL

Storage : In dark and at room temperature  
Expiry date : April 1996  
Disposal : Incineration

elf atochem



Port-de-Bouc/Fos

PORT DE BOUC, LE 26/09/95

## CERTIFICAT D'ANALYSE

NATURE DE PRODUIT : BROMURE D'ISOAMYLE  
DATE DE L'EXPEDITION :  
DESTINATAIRE : CAL (Mr BOURALY)  
TRANSPORT : 200 g

-----  
LOTS N° : 4-153-1

ANALYSE :

Somme des légers %	=	0.40
Alcool %	=	0.14
BIA %	=	99.1
BIP	=	0.06
Bromure d'allyle %	=	0.03
Somme des lourds%	=	0.25

EAU mg/kg	=	240
ACIDITE (HBr) mg/kg	=	< 10
COLORATION U.H	=	< 10

LE RESPONSABLE LABORATOIRE

  
JL.REYNAUD

2. Diet formula

Ref: A04

**COMPLETE DIET****RAT AND MOUSE MAINTENANCE DIET**

Appearance: 15 mm diameter pellets or powder

Conditioning: 25 kg double paper bag with aluminium on the outside

Daily portion: Rat 18-25 g, Mouse 5-10 g, water *ad libitum*.**FORMULA %**

Cereals and cereal biproducts .....	88
Vegetable protein (soya bean meal, yeast) .....	7
Animal protein (fish) .....	2
Vitamin and mineral mixture .....	3

**AVERAGE ANALYSIS %**

Calorific value (KCal/kg) .....	2900
Moisture .....	12
Proteins .....	17
Lipids .....	3
Carbohydrates (N.F.E.) .....	58.7
Fibre .....	4
Minerals (ash) .....	5

**AMINO ACID VALUES  
(calculated in mg/kg)**

Arginine .....	9800
Cystine .....	2300
Lysine .....	8500
Methionine .....	3200
Tryptophan .....	1900
Glycine .....	8100

**FATTY ACID VALUES  
(calculated in mg/kg)**

Palmitic acid .....	2600
Palmitoleic acid .....	Traces
Stearic acid .....	500
Oleic acid .....	8000
Linoleic acid .....	14500
Linolenic acid .....	Traces

**MINERALS (calculated in mg/kg)**

	Nat val.	CMV val.	Total
P .....	5900	0	5900
Ca .....	3300	5000	8300
K .....	6700	0	6700
Na .....	300	1600	1900
Mg .....	1900	100	2000
Mn .....	50	40	90
Fe .....	90	150	240
Cu .....	15	15	30
Zn .....	40	45	85
Co .....	T	1.5	1.5
I .....	0.3	0	0.3

**VITAMINS (calculated per kg)**

	Nat val.	CMV val.	Total
Vitamin A	Traces	7500 IU	7500 IU
Vitamin D3	Traces	1500 IU	1500 IU
Vitamin B1	6 mg	1 mg	7 mg
Vitamin B2	2 mg	4.5 mg	6.5 mg
Vitamin B3	10 mg	6.5 mg	16.5 mg
Vitamin B6	1.3 mg	1.3 mg	2.6 mg
Vitamin B12	0.01 mg	0.01 mg	0.02 mg
Vitamin E	15 mg	15 mg	30 mg
Vitamin K3	0.25 mg	2.25 mg	2.5 mg
Vitamin PP	60 mg	15 mg	75 mg
Folic acid	0.5 mg	0 mg	0.5 mg
Biotin	0.04 mg	0 mg	0.04 mg
Choline	1200 mg	400 mg	1600 mg

Available under quality "Control Ref.: A04 C "

U.A.R., 7 rue Galliéni, 91360 Villemoisson - Tel: 69.04.03.57 - Fax : 69.04.81.97  
(Ref. Doc. UAR: 1992)

### CERTIFICATE OF AUTHENTICITY

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