

BASF Corporation

8EHQ 0695-13472

**BASF**

RECEIVED  
OPPT CBIC

Certified Mail  
Return Receipt Requested

95 JUN 20 AM 11:12

June 13, 1995

8EHQ-0695-13472

Document Processing Center (TS-790)  
Attention: 8(e) Coordinator  
Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
401 M Street, SW  
Washington, DC 20460

**ORIGINAL**

**Contains No CBI**

Ladies and Gentlemen:

Subject: Notice in Accordance with Section 8(e) of TSCA - Acute Toxicity  
Studies with Cyclohexanone Oxime (CAS No. 100-64-1).

BASF Corporation is submitting recently received toxicity studies of cyclohexanone oxime (CAS No. 100-64-1), conducted by BASF Aktiengesellschaft, Ludwigshafen, Germany. Although BASF Corporation does not feel that the information presents a substantial risk to health or environment, it is being submitted under Section 8(e) of TSCA.

Attached is an English translation of the original German studies. The 1967 report indicated that cyclohexanone oxime, when administered intravenously to rabbits and perorally to cats and dogs, caused narcosis at doses ranging from 100 mg/kg in rabbits (iv) to 2000 mg/kg in dogs (oral). Narcotic effects lasted from 27 minutes in rabbits to 26 hours in dogs; other symptoms, such as apathy, were reported in dogs at 4 days.

BASF Corporation understands that the reporting of these results under TSCA 8(e) is in accordance with EPA's policy. Please note that this submission does not contain confidential business information.

If you have any questions, please feel free to contact me at (313) 246-6207.

Very truly yours,

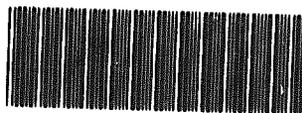
BASF CORPORATION

Edward J. Kerfoot, Ph.D.  
Director, Toxicology & Product Regulations



8EHQ-95-13472  
INIT 06/20/95

/Attachment



88950000256

95 JUN 30 AM 8:12  
RECEIVED  
OPPT CBIC

Occupational Hygiene - Pharmacological Institute of the BASF

Vers. no. XVII 2 6 9

Your reference: Dr. Ka/H

Your letter of 7/26/67

Received 8/4/67

Distribution: Medical Department

Confidential  
to FARO Department  
via Dir. Dr. Daumiller  
Division V

Subject product: Cyclo-hexanon-oxime, technical  
(solid)

Chemical designation: (formula, composition)

Benz-NOH  $C_6H_{11}ON$

Internal intermediate product  
Component of baked-on lacquers

#### RESULT OF THE PRELIMINARY OCCUPATIONAL TOXICOLOGICAL TEST

According to the structure of the product and according to studies, whose individual results are listed on page 2 of this report, cyclo-hexanon-oxime, technical needs no warning labels for transport and processing.

#### Note:

The result of the preliminary toxicological test and the structure of the product provide no information about possible damage from the repeated action of small amounts. For the time being, cyclo-hexanon-oxime, technical, can be processed with the usual precautionary measures.

The findings of the present study more or less correspond to the results which Prof. Gross communicated in his report of January 31, 1939 relating to cyclo-hexanon-oxime (= Aceta 600), also to our findings of December 28, 1956.

Further studies are anticipated.

Ludwigshafen, Sept. 15, 1967

[Signatures]

(OETTEL) (ZELLER)

This report is the property of BASF Ludwigshafen

Occupational Hygiene - Pharmacological Institute of the BASF  
Result of the preliminary occupational toxicological test of 9/5/67

Substance: cyclo-hexanon-oxime, technical      Vers. No. XVII 2 6 9

Acute toxicity:      Approximate average lethal dose = A LD 50      A LD 50 per kg body weight, observation period 7 days

Form of applications: 10 and 30% aqueous traganth solution  
Mouse i.p. about 1.0 g  
Rat p.o. about 3.2 g

Symptoms: Dyspnoea, severe staggering, apathy, abdominal and lateral position

Section: Rats, no finding, mice: adhesions and fusions in the abdominal space

Signed: Dr. Zeller

Acute inhalation toxicity (rats = R; guinea pigs = Me; mice = Ma)

Inhalation of an atmosphere saturated with steam at x °C. For saturation, conducted through a layer of the product. For saturation, the air is conducted through a layer of the product about 5 cm high.

Exposure time:

	3'	10'	30'	1 h	3 h	8 h	
a) Steam at 20°C (R)	-	-	-	-	-	0/12	Mortality x/y
b) Steam at 120°C (R)	4	hours" x)	0/6				Deceased/exposed animals
c) Dust							
d) Spray							
% in							

x) After four hours, the product was sublimed away into the infeed system

Symptoms: None  
Section without finding

Signed: Dr. Hoffman

Skin scratch (Rabbits)                      Action time                      Finding after 24 hours                      Finding after 8 days

Application form:	Back	1'		
80% aqueous rubbed-in material	Back	5'		
	Back	15'	none	none
	Back	20 h		
	Ear	20 h		

Scratch in the mucous membrane (rabbit eye)

Finding after 1 hour                      Finding after 24 hours                      Finding after 8 days

Application form:			
(1 x 50 mm <sup>3</sup> ) unchanged	R+/Ö	R++/Ö++/isolated small hemorrhages	none
Comparison talc	R+	R++/Ö++/Tr+	none

Explanation of symbols for scratch on the skin and mucus membrane:

R = reddening, Ö = edema, Sh = scaling, N = necrosis, Tr = cloudiness, Na = scar, (+) questionable, + = slight, ++ = strong, +++ = very strong, φ = no irritation

Signed Dr. Zeller

This report is the property of BASF Ludwigshafen and may be transmitted or published only with express approval.

BASF  
Occupational Hygiene - Pharmacological Institute

To  
Main Laboratory  
Dir. Prof. Dr. Reppe

Our references: VI/4, VI/401 Ludwigshafen on the Rhine, December 28, 1956 / z

Report of the pharmacological test of the narcotic effect of cyclo-octanon-oxime and cyclo-hexanon-oxime

In the course of the occupational-toxicological investigation of cyclo-hexanon-oxime, in connection with determining its toxicity, a relatively strong narcotic effect of the product appeared, even after peroral administration to cats (see our report of November 3, 1955, our test number IV/268). For this reason, we have presented a more precise pharmacological test of this effect for discussion. As desired by the manufacturer, we first performed special studies of the narcotic effect.

For comparison, the cyclo-hexanon-oxime, which is produced in the plant on a technical scale, is tested concomitantly, and the results of our tests on the following commercial products are presented:

- 1.) Valamin = ethinyl-cyclohexanol-carbamate
- 2.) Sodium evipan = sodium salt of N-methyl-cyclohexenyl-methyl-barbituric acid

EXPERIMENTS

Methodology: The methodological procedure for the investigation in the rotary drum, for the determination of the stages of narcosis and of toxicity corresponds to that of a previous test (compare our expert opinion of December 6, 1955, our Vers. No. IV/440-444). In contrast to the results with cyclo-octanon-oxime, which were reported on November 3, 1955, we now administered the products in a traganth emulsion for the peroral administration, so as to eliminate any effect of the solvent itself. For intravenous administration, the substances were dissolved in Lutrol.

I. HYPNOTIC EFFECT AND TOXICITY

1.) Mice and Rats

The following table shows the results of the tests with mice:

Product	LD 50 mg/kg	Sedative ED 50 mg/kg	Sed. ED 50 = X % of LD 50	Narcotic ED 50 mg/kg	Narc. ED 50 = X % of LD 50
<u>Mouse i.p. (Traganth emulsion):</u>					
Cyclo-octanon-oxime	ca. 600	ca. 100	17%	ca. 200	33%
Cyclo-hexanon-oxime	ca. 900	ca. 250	28%	ca. 400	44%
Valamin	360	46	13%	100	28%
Evipan	280	24	9%	80	28%
<u>Mouse p.o. (Traganth emulsion)</u>					
Cyclo-octanon-oxime	ca. 1000	ca. 200	20%	ca. 400	40%
Cyclo-hexanon-oxime	ca. 2000	ca. 600	30%	ca. 1000	50%
Valamin	ca. 1100	100	11%	200	18%
Evipan	750	90	12%	250	33%

**RESULTS:**

With parenteral administration, the same effect from cyclo-octanon-oxime requires about twice the dose of valamin and 2.5 to 4 times the dose of Evipan-Na. However, the therapeutic breadth is not much smaller than with the comparison substances.

With peroral administration, about twice the doses are required with cyclo-octanon-oxime compared to valamin and Evipan. However, here the therapeutic breadth is less favorable compared to the commercial preparations.

Cyclo-hexanon-oxime was tested only by way of orientation. With both forms of the administration it had only about one half to one third of the effective strength of cyclo-octanon-oxime. Its therapeutic breadth is also less favorable.

The average lethal dose of cyclo-octanon-oxime for rats is about 1000 mg/kg per os (as traganth emulsion). This is of the same order of magnitude as with mice.

**2.) In rabbits****a) In intravenous administrations (10% in Lutrol)**

The duration of the lateral position and the toxicity of the individual animals is shown in the following table:

Product	Dose mg/kg	Duration of the lateral position (LP)	Course
Cyclo-octanon-oxime	30	1 min	Survives
	50	14 min 13 min 13 min	Survives Survives Survives
	60	12 min	Survives
	80	28 min 35 min instant LP	Survives Survives Exitus after 4 min
	100	instant LP	Exitus after 5 min
Cyclo-hexanon-oxime	100	No LP, slight staggering	Survives
	200	4 min 6 min	Survives Survives
	300	ca. 27 min ca. 7 min (2 animals)	Sacrificed after 4 1/2 h Survives
Evipan-Na in 0.9% NaCl	20	5 min	Survives
	30	20 min (average value of 6 animals)	Survives
	40	33 min (average value of 3 animals)	Survives
	50	27 min (one animal)	Instant Exitus (2 animals)

### RESULTS:

For narcosis lasting about as long as after 30 mg/kg Evipan, about 60 mg/kg of cyclo-octanon-oxime are needed. The therapeutic breadth is about the same for both products.

Cyclo-hexanon-oxime is also much weaker in the case of rabbits and is effective only for a very short time.

The onset of narcosis occurs during the injection with both products. The deterioration of octanon-oxime is relatively fast. Repeated injection after about one hour did not always exhibit a clear extension of the duration of the narcosis, as the following table shows:

Product	Dose	Duration of the lateral position	Course
Cyclo-octanon-oxime	30 mg/kg after 45' 70 mg/kg	1 min	Immediate Exitus
	50 mg/kg after 60' 60 mg/kg	13 min 9 min	Survived
	50 mg/kg after 70' 50 mg/kg	16 min 30 min	Survived
	60 mg/kg after 50' 80 mg/kg	12 min	Immediate Exitus
	80 mg/kg after 75' 80 mg/kg	23 min	Immediate Exitus

b) With peroral administration (as traganth emulsion):

Product	Dose mg/kg	Symptoms	Course
Cyclo-octanon-oxime	316 500 800 1000 1000	No narcosis, only staggering gait Lateral position (LP) for 17 min Lateral position (LP) for 27 min Lateral position (LP) for >7 hours Lateral position (LP) for >6 hours	Survived Survived Survived Exitus after 25 hours Exitus after 6 hours
Cyclo-hexanon-oxime	1000 1000 2000	No LP, only staggering LP for about 2 hours, inappetence for 2 days, no methb. in the blood after 24 and 72 hours LP and narcosis	Exitus after 25 hours Survived Exitus after 25 hours
Valamin	300	Several hours LP	Survived
Evipan	1000		

x) Section finding: mucous membrane, musculature, lungs, heart, liver, kidneys, spleen all black-brown color; blood coffee brown

**RESULTS:**

Lateral position lasting several hours can be achieved after peroral administration of both products only with toxic doses. In about half its lethal dose, cyclo-octanon-oxime still results in a brief lateral position, while cyclo-hexanon-oxime exhibits no narcotic effect. By contrast, Valamin caused narcosis for several hours already with half the threshold dose of cyclo-octanon-oxime.

## 3.) Cats with peroral administration (as traganth emulsion)

Product	Dose mg/kg	Symptoms	Course
Cyclo-octanon-oxime	500	Deep narcosis for more than 9 hours ; after 24 hours, still LP. Animal wakes up.	Exitus after 26 1/2 hours
	500	No deep narcosis	Survives
	800 800	Deep narcosis Deep narcosis	Exitus after 30 min Exitus after 45 min
Cyclo-hexanon-oxime	1000	No deep narcosis, LP only for about 30 minutes, while the animal is still moving somewhat	Survives
	2000	Narcosis	Exitus after 2 1/2 hours
Valamin	50	Deep narcosis for several hours	Survives
Evipan	50	LP but no deep narcosis	Survives
	100	Deep narcosis for more than 8 hours	Survives
	100	Deep narcosis for several hours	Survives

## 4.) On dogs after peroral administration (as traganth emulsion)

Cyclo-octanon-oxime	500	Staggering, sleepiness, animal can be wakened again at any time	Survived
	1000	Deep narcosis for > 7 hours, can get up after 24 hours, but is still staggering severely. Tests of liver function (bromosulfophthalein test) after 8 days, without finding	
	2000	Deep narcosis for about 24 hours	
Cyclo-hexanon-oxime	1000	Deep narcosis for more than 6 hours, after 21 hours still staggering, sometimes still apathetic over the next 4 days, eats poorly. After 24 and 48 hours, no methb can be detected in the blood	
	1000	LP for about 4 hours; after 24 hours no finding, no methb.	
	2000	Deep narcosis for about 26 hours	
Valamin	100	Deep narcosis for about 2 hours	
Evipan	100	Deep LP for 8 hours	

To further confirm the in-vivo hemolysis effect, the erythrocyte resistance was determined before and after the injection with one animal. The comparison values are shown in the following table:

	% NaCl Solution		
	Before injection	2 hours after injection	27 hours after injection
Beginning hemolysis	0.5	0.9	0.6
Complete hemolysis	0.55	0.39	0.36

#### RESULTS:

In contrast to cyclo-octanon-oxime, which was investigated only at much smaller doses due to its stronger effect, cyclo-hexanon-oxime in high doses administered parenterally and probably also perorally (see Section finding after 1000 mg/kg, page has a conspicuous hemolysis effect.

#### IV. CHANGE OF THE EFFECTIVENESS OF CYCLO-OCTANON-OXIME DURING EXTENDED STORAGE

The main portion for the present studies was performed about one half year after the substance was produced. In a supplementary study after another half year, the same cyclo-octanon-oxime, after intravenous administration in rabbits, was much more toxic.

While 50 mg/kg previously were always survived, now three out of four rabbits died within 3 to 10 minutes, with the appearance of a deep narcosis. The last animal died following an injection with the same dose, repeated after one hour. Even 30 mg/kg caused death in one animal within 5 minutes. On the other hand, 10 mg/kg at hourly intervals could be administered to a rabbit six times in succession without resulting in narcosis-like symptoms.

According to a telephone communication from Dr. Rapp, the UR [sic, but should be either IR or UV] spectrum also shows certain changes after the product has been stored for an extended time.

It is planned to study the narcotic effect of freshly made cyclo-hexanon-oxime together with cyclo-octanon-oxime.

#### EVALUATION

Cyclo-hexanon-oxime and cyclo-octanon-oxime, even when administered perorally to mice, rats, cats, and dogs, exhibit a narcotic effect. Except for dogs, the effect of 4loctanon-oxira was far superior to that of hexanon-oxime. In comparison to the commercial preparations Valamin (ethinyl-cyclohexanol-carbamate) and Evipan (N-methyl-cyclohexanyl-methyl-barbituric acid) the effect of cyclo-octanon-oxime on mice is relatively strong, the effect on higher animals (cats and dogs), however, it is much weaker.

Comparison studies with cyclo-octanon-oxime 1/2 year later showed a clear increase of the toxicity of the product with parenteral administration. Since the specimen of the substance had already been stored for 1/2 year prior to the study, the present test results possibly may not be identical to those obtained from freshly made-up product. The reason for these changes must be clarified by chemical studies.

After high parenteral and probably also peroral doses, cyclo-hexanon-oxime resulted in strong hemolysis phenomena in vivo. These could not be detected with cyclo-octanon-oxime.

As far as we know, the narcotic effect of oximes has not yet been reported in the literature. Since factory products are involved, which are already being produced on a technical scale in another connection, it seems appropriate to continue work in this field. Since the strength of the effect seems to depend both on the oxime structure and on the ring system, we propose to transmit possibly still available or easily producible dioximes or further substituted derivatives of cyclo-octanon-oxime for investigation. However, tests relating to the durability of the substance and to chemical changes upon extended storage of the substance would have to be performed first.

[Signatures]

(Prof. Dr. med. H. OETTEL) (Dr. med. W. FÖRSTER)

**Best Available Copy**