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Subject: Acute Oral Toxicity (LD_{50}) Study with Pyridate in Rats [Note: Study Conducted Using OECD Guidelines.]

Test Material: Pyridate, Technical (90.3%).

Accession Number: 073280

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co., Ag., Switzerland

RCC Project Number: 036990

Testing Period: September 18-October 17, 1984

Report Submitted to Sponsor: October, 1984

Materials and Methods:

Male and female KFM-Han Wistar (outbred, SPF-quality) rats, 8 to 11 weeks old, weighing between 149 and 247 g were acclimated under laboratory conditions for 7 days prior to treatment. The animals were housed in Makrolon type-3 cages, 5 per cage and kept in an animal room with controlled temperature, humidity and light. Food and water were available ad libitum.

The test article was prepared as a suspension (weight by volume) using the vehicle polyethyleneglycol 400. All preparations were made immediately prior to dosing and their homogeneity was maintained during treatment using a magnetic stirrer. The animals were divided into 4 groups (5 males and 5 females each) and after being fasted for 12 to 18 hours, each group was administered orally one of four test article concentrations (1,000, 3,000, 5,000 and 8,000 mg/kg in a total volume of 10, 20, 20, and 20 mL/kg, respectively).

Treated animals were observed for signs of toxicity and mortality 4 times during day 1 and once daily during days 2 to 15. Individual body weights were recorded on day 1 just prior to dosing and on days 8 and 15 after dosing. Necropsies were performed on all experimental animals that either died during the observation period or were sacrificed at the end of the study. The LD_{50} values were estimated using a LOGIT-model.

Results:

All male and female animals treated with the lowest concentration (1,000 mg/kg) survived until the end of the observation period. The only sign of toxicity observed in this group was slight dyspnea during the first few hours after dosing. All animals treated with this low dose gained weight

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during the course of the study.

Treatment of rats with 3,000 mg/kg body weight resulted in the mortality of 1 male and 3 female animals. All animals exhibited signs of toxicity consisting mainly of severe sedation, dyspnea and ataxia, curved body position, and ruffled fur. These toxicity signs were predominantly present within a few hours after dosing. Individual body weights of the surviving animals increased during the course of the study.

Treatment of rats with 5,000 mg/kg body weight resulted in the mortality of 1 male and 4 female animals. Toxicity symptoms observed in this treatment group were the same (and generally of the same intensity) as those reported above for the 3,000 mg/kg treatment group. All surviving animals gained weight during the study.

Administration of the test article at 8,000 mg/kg body weight resulted in the mortality of 4 male and 3 female animals. The observed toxicity signs and severity were the same as those reported for the lower treatments (3,000 or 5,000 mg/kg). The surviving animals gained weight during the study.

The LD_{50} values were estimated for each sex or both sexes combined, from the following mortality table:

Dose mg/m^3	No. dead M	No. dead F	% Mortality M	% Mortality F	No. dead M&F	% Mortality M&F
1,000	0	0	0	0	0	0
3,000	1	3	20	60	4	40
5,000	1	4	20	80	5	50
8,000	4	3	80	60	7	70

LD_{50} - Males = 5993 mg/kg (95% CL 3164 - 33610 mg/kg)

Females = 3544 mg/kg (95% CL 871.0 - 8848 mg/kg)

Male & Female = 4690 mg/kg (95% CL 2945 -9034 mg/kg)

Gross necropsies were performed on all animals in the study. Animals that survived until termination of the study did not reveal any pathologic changes in any of the organs examined. Animals that died during the study revealed some pathologic

changes and are listed below separately for each treatment group:

1. 3,000 mg/kg - slight reddened intestines and/or stomach; mottled lung.

2. 5,000 mg/kg - stomach, slight corrosion; intestines slight reddened and slight meteorism; lung, dark-red discolored, mottled.

3. 8,000 mg/kg - stomach/intestines, slightly reddened with slight or severe meteorism; lung mottled; small intestines, slightly reddened; stomach/intestines filled with fluid, severe.

Conclusions:

The $AOLD_{50}$ for pyridate technical (90.3% pure) in male and female Wistar rats was estimated to be 4690 mg/kg with 90 percent confidence limits of 2945 to 9034 mg/kg.

Classification: Core-guideline

Category of Toxicity: III

Subject: Acute Dermal Toxicity (LD_{50}) Study with Pyridate in Rabbits [Note: Study Conducted Using OECD Guidelines.]

Test Material: Pyridate, Technical (90.3%

Accession Number: 073280

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co., Ag., Switzerland

RCC Project Number: 037001

Testing Period: September 18-October 2, 1984

Report Submitted to Sponsor: October, 1984

Materials and Methods:

Five male and 5 female New-Zealand White rabbits (Kleintierfarm Madoerin, Ag. Switzerland), 15 to 16 weeks old and weighing between 2.0 and 2.9 kg each were acclimated under laboratory conditions for 7 days prior to treatment. The animals were housed individually in stainless steel cages, equipped with an automatic cleaning and drinking system, and kept in an animal room with controlled temperature, humidity, and light. Food and water were available ad libitum.

Approximately 24 hours before treatment, the backs of the animals were shaved exposing an area of approximately 40 cm^2. The test article was applied to the exposed skin at a single dose level of 2,000 mg/kg (in a total volume of 2 mL/kg) and covered with an occlusive dressing (wrapped around the abdomen) which was held in place by an elastic adhesive bandage. The dressing was removed from the skin 24 hours after the application, the skin flushed with lukewarm water and the skin reaction was assessed according to the method of Noaks and Sanderson ("a method of determining the dermal toxicity of pesticides").

Treated animals were observed for signs of toxicity and mortality 4 times during day 1 and once daily during days 2 to 15. Individual body weights were recorded immediately prior to treatment (day 1) and on days 8 and 15 after treatment. Necropsies were performed on all treated animals at the termination of the study (day 15).

Results:

Male and female rabbits treated with the test article

survived until termination of the study. Two animals, a male and a female, lost weight during the study. The male rabbit lost approximately 27 percent of its body weight from day 8 to 15, while the female rabbit lost 4 percent of its body weight from day 1 to day 8 but gained weight from day 8 to day 15. All other animals gained weight during the study. No other systemic symptoms were observed in any of the animals. Skin irritation, in the form of slight to moderate erythema and edema, was observed in all male and female treated animals from day 2 to day 15 of the observation period.

Necropsies performed on all animals at termination of the study revealed the following pathologic changes:

Lung, dark-red, mottled (1 male and 2 females); lung, dark-red areas, mottled (1 male and 1 female); lung, dark-red, mottled, severe, foam excretion (1 female).

Conclusions:

The $ADLD_{50}$ for pyridate, technical (90.3%) in male and female New Zealand White rabbits was determined to be greater than 2,000 mg/kg body weight.

Classification: Core-guideline

Category of Toxicity: III

Subject: Acute Aerosol Inhalation (LC_{50}) Toxicity Study (4-Hour Exposure) with Pyridate in Rats [Note: Study Conducted Using OECD Guidelines.]

Test Material: Pyridate, Technical (90.3%)

Accession Number: 073280

Sponsor: Chemie Linz Ag., Austra

Testing Facility: Research & Consulting Co., Switzerland

RCC Project Number: 016255

Testing Period: April 12-27, 1983

Report Submitted to Sponsor: May, 1983

Materials and Methods:

Ten male and 10 female outbred Wistarstock (SPF Han.) rats, 7to 9 weeks old, weighing between 185 to 280 g each were acclimated for 7 days under laboratory conditions prior to treatment. The animals were housed (in groups of 5) in Makrolon type-4 cages with food and water available ad libitum. The animals were kept in a room with controlled temperature, relative humidity and light.

Each group of rats was exposed to either 2,700 or 4,370 mg of pyridate/M^3 for 4 hours. Exposures were conducted in 100-liter polyvinylchloride nose-only chambers where only the snouts and the nostrils of the animals were exposed to the aerosol. The air flow was maintained at 10 L/minute and the air pressure was 3 atmospheres. The exposure concentrations were determined gravimetrically at regular intervals using selectron filters. Aerosol particle size was determined gravimetrically on selectron filters with the aid of 4-stage cascade impactor (Casella Ltd., London, England). The temperature, relative humidity and oxygen content in chamber air were also monitored during exposure.

Treated animals were observed for signs of toxicity and/or mortality five times during the first day and daily thereafter. Body weights were recorded on day 1 (just prior to exposure) and on days 8 and 15 postexposure. At termination of the study (day 15) all surviving animals were killed by exsanguination and subjected to necropsy.

Results:

Concentrations of the test article in the exposure chambers were determined (from 5 gravimetric samples) to be 2,700 $\pm$ 110 mg/M^3

and 4,370 ± 364 mg/M^3. Approximately 66 percent of the sampled particles from the 2,700 mg/M^3 group and 70 percent from the 4,370 mg/M^3 group, were found to have a particle size distribution of 7 microns or less.

All male and female animals exposed either to the low or the high dose level of the test article survived until termination of the study. All groups of animals appeared to gain weight at a slower rate within 7 days after exposure but weight gain from day 8 to 15 appeared to be normal (no controls were used for comparison).

Toxic signs were seen in both sexes of animals exposed to either the low or the high concentration of the test article and included: sedation, dyspnea, curved body position and ruffled fur. All signs were of slight to moderate intensity and were predominantly present between 3 and 24 hours after exposure.

Necropsies were performed on all animals in the study. The only pathological change reported was mottled, dark-red lungs in 3 out of 5 male and 2 of 5 female animals in the 2,700 mg/M^3 group and 3 out of 5 male and 3 out of 5 female animals in the 4,370 mg/M^3 group.

Conclusions:

The AILC$_{50}$ for Pyridate Technical expressed as gravimetric concentration was determined to be greater than 4,370 mg/M^3 in both sexes of Kfm:Wistar (SPF Han.) strain rats.

Classification: Core-Minimum

Category of Toxicity: III

Subject: Irritant Effects of CL-11344 on Rabbit Eye Mucosa

Test Material: Pyridate (CL-11344)

Accession Number: 072340

Sponsor: Chemie Linz, A.G., Austria

Testing Facility: Huntingdon Research Centre, Huntingdon, England

Study Number: 6528/D12/76

Report Submitted to the Sponsor: September 1976

Methods and Materials:

The authors did not describe the procedure used for conducting the present study. Instead, they attached a transcript of the procedure employed as prescribed by the Consumer Product Safety Commission of the U.S.A. in the Code of Federal Regulations Title 16, Section 1500.42. A guide for grading eye irritation (for cornea, iris, and conjunctivae) was also attached. However, it is not clear from the report whether the guidelines were followed and to what extent. Also, it is not clear as to the strain or sex of animals used or animal maintenance during the 21-day observation period.

Results:

The numerical scores awarded to the ocular reactions elicited by CL-11344 are shown in table 1 (abstracted from the original report). The results show that in one of six animals used a positive reaction was seen in the cornea (dulling of the cornea) beginning with day 1 posttreatment and lasting through day 21 (termination of the study). Another animal exhibited mild conjunctiva (redness) in the first 48 hours of the study but this effect was reversed (disappeared) by the third day postexposure.

Conclusions:

Under the conditions of this study only one rabbit exhibited positive reactions to CL-11344 treatment. Thus, CL-11344 is considered a nonirritant when administered to the rabbit eye at a dose of 0.1 mL.

Category of Toxicity: IV

Classification:

The present study is classified as Core-Supplementary due to: (1) The test article was not clearly identified and its purity was not specified. (2) No pharmacological or toxicological signs in test animals were reported. (3) The pH of the test solution was not specified.

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TABLE 1

Numerical scores awarded to the ocular reactions elicited by CL 11.344

ANIMAL NUMBER	REGION OF EYE		DAY 1	2	3	4	7	14	21	Positive (+) or Negative (-) Result
1	Cornea		0	0	0	0	0			-
	Iris		0	0	0	0	0			
	Conjunctiva	Redness	0	0	0	0	0			
		Chemosis	0	0	0	0	0			
2	Cornea		D	D	D	D	D	1	1	+
	Iris		0	0	0	0	0	0	0	
	Conjunctiva	Redness	0	0	0	0	0	0	0	
		Chemosis	0	0	0	0	0	0	0	
3	Cornea		0	0	0	0	0			-
	Iris		0	0	0	0	0			
	Conjunctiva	Redness	0	0	0	0	0			
		Chemosis	0	0	0	0	0			
4	Cornea		0	0	0	0	0			-
	Iris		0	0	0	0	0			
	Conjunctiva	Redness	1	1	0	0	0			
		Chemosis	0	0	0	0	0			
5	Cornea		0	0	0	0	0			-
	Iris		0	0	0	0	0			
	Conjunctiva	Redness	0	0	0	0	0			
		Chemosis	0	0	0	0	0			
6	Cornea		0	0	0	0	0			-
	Iris		0	0	0	0	0			
	Conjunctiva	Redness	0	0	0	0	0			
		Chemosis	0	0	0	0	0			

D = Dulling of the cornea

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GRADES FOR OCULAR LESIONS

From: "Illustrated Guide for Grading Eye Irritation by Hazardous Substances"
U.S. Department of Health, Education and Welfare, Food and Drug Administration
Washington, D.C. 20204

Cornea	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	(1)*
Easily discernible translucent areas, details of iris slightly obscured	2
Nacreous areas, no details of iris visible, size of pupil barely discernible	3
Complete corneal opacity, iris not discernible	4
Iris	
Normal	0
Markedly deepened folds, congestion, swelling, moderate circumcorneal injection (any of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive)	(1)*
No reaction to light, haemorrhage, gross destruction (any or all of these)	2
Conjunctivae	
Redness (Refers to palpebral and bulbar conjunctivae excluding cornea and iris)	
Vessels normal	0
Some vessels definitely injected	1
Diffuse, crimson red, individual vessels not easily discernible	(2)*
Diffuse, beefy red	3
Chemosis	
No swelling	0
Any swelling above normal (including nictating membrane)	1
Obvious swelling with partial eversion of lids	(2)*
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

* Bracketed figures indicate lowest grades considered positive under Title 16, Section 1500.42 of the Code of Federal Regulations

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Subject: Irritant Effects of CL-11344 on Rabbit Skin

Test Material: Pyridate (CL-11344)

Accession Number: 072340

Sponsor: Chemie Linz, A.G., Austria

Testing Facility: Huntingdon Research Centre, Huntingdon, England

Study Number: 6527/11D/76

Report Submitted to the Sponsor: September 1976

Methods and Materials:

A description of the procedures used in conducting the present study was not reported. The authors, however, attached a transcript of the procedure employed as "prescribed by the Consumer Product Safety Commission of the U.S.A. in the Code of Federal Regulations, Title 16, Section 1500.41." This procedure and the scoring system used in testing primary irritant substances is given here as Appendix. It is not clear from the report as to the strain or sex of the six animals used. Also, no information was reported concerning the maintenance of the experimental animals.

Results:

The numerical scores awarded to the dermal reactions elicited by Pyridate (CL-11344) are presented in table 1 (abstracted from the original report). The results show that all six animals developed a very slight to well-defined erythema in both the intact and the abraded sites at the 24-hour reading. At the 72-hour reading very slight to moderate erythema was seen. All animals also developed very slight to slight edema in intact and abraded skin at the 24-hour reading and very slight to moderate edema at the 72-hour reading. The overall irritation index was calculated to be 3.3.

Conclusion:

The primary irritation index for Pyridate on rabbit skin was calculated to be 3.3. Thus, Pyridate is considered to be a moderate irritant.

Category of Toxicity: III

Classification:

The present study is classified as Core-Supplementary mainly because the test article was not clearly identified and its purity was not specified.

004939

Subject: Acute Oral Toxicity (LD_{50}) Study in Rats with CL-11344/216 EC [Note: Study conducted using OECD Guidelines.]

Test Material: CL-11344/216 EC (45.7% ai; 3.75 EC)

Accession Number: 073307

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co., Ag., Switzerland

RCC Project Number: 037607

Testing Period: October 23 to November 13, 1984

Report Submitted To Sponsor: November 1984

Materials and Methods:

Male and female, KFM-Han Wistar (outbred SPF-quality) rats 8 to 12 weeks old, weighing between 167 and 252 g were used in this study. All rats were acclimated for 7 days under laboratory conditions before the initiation of the study. The animals were kept in Makrolon type-3 cages with softwood bedding (5 animals/cage) with food (Kliba 343) and water available ad libitum. The cages were placed in a room with controlled temperature (22 + 2 °C), humidity (55 ± 10%), and light (12 hour light/dark cycle).

The test article was prepared as a suspension (weight by volume) using a 2 percent solution of carboxymethylcellulose natriumsalt purum, in distilled water. All preparations were made immediately prior to dosing and their homogeneity maintained during treatment using a magnetic stirrer. The test preparation was administered to rats of both sexes (five male and five female) by oral gavage at dose levels of 400, 1000, or 5000 mg/kg in a total volume of 10 mL/kg body weight (20 mL at 5000 mg/kg). Animals were fasted for 12 to 18 hours prior to compound administration.

Treated animals were observed for toxicity and mortality four times during day 1 and once daily during days 2 through 15. Individual body weights were recorded just prior to dosing (day 1) and on days 8 and 15 after treatment. Necropsies were performed on all animals that either died during the observation period or were sacrificed at the end of the study.

Results:

All male and female animals treated with the test article at 400 mg/kg survived throughout the study. The toxicity symptoms observed in these animals consisted mainly of sedation, moderate

dyspnea, curved body position, and ruffled fur. All animals on this treatment gained weight during the course of the study.

No mortality was observed when male rats were treated with 1000 mg/kg of the test article. However, with the same treatment (1000 mg/kg) four (out of five) female rats died within 24 hours posttreatment. Within 5 hours after treatment, male and female animals exhibited signs of toxicity which included severe sedation, dyspnea, ataxia and spasms, and curved body position. As was the case with the lower dose level, all animals that survived the duration of the study gained weight. Whether the weight gain was within normal limits or not cannot be determined since vehicle controls were not used in this study. However, weight gains between the low and mid dose males were comparable, as were the weight gains between the low and mid dose females.

All animals treated with 5000 mg/kg of the test article died within 24 hours after treatment with most of the deaths occurring within 3 hours posttreatment. Prior to death, all animals exhibited signs of severe toxicity as seen with the medium dose (1000 mg/kg) with additional toxicity consisting of coma and diarrhea.

Gross pathology was performed on all animals in the study. Animals that survived until termination of the study did not reveal any pathologic changes in any of the organs examined. The four female animals on the medium dose that died have shown the following pathologic changes: intestines reddened, stomach reddened, and lung and liver mottled. Pathologic changes observed with animals that died on the high dose group (5000 mg/kg) included the following: stomach/intestines reddened, filled with test article, meteorism.

The LD_{50} values were estimated for each sex or both sexes combined, from the following table:

Dose mg/kg	# dead M	# dead F	% dead M	% dead F	Total M&F	% Total M&F
400	0/5	0/5	0	0	0/10	0
1000	0/5	4/5	0	80	4/10	40
5000	5/5	5/5	100	100	10/10	100

LD_{50} - Male rat = 1871 (95% CL 941-6339) mg/kg

LD_{50} - Female rat = 905 (95% CL 206-1999) mg/kg

LD_{50} - Male and Female = 1258 (95% CL 814-2074) mg/kg

Conclusions:

The AO LD_{50} for CL-113344/216 EC in male and female Wistar rats was determined to be 1258 mg/kg with 95 percent confidence limits of 814-2074 mg/kg.

Classification: Core-Guideline

Category of Toxicity: III

004939

Subject: Acute Dermal Toxicity (LD_{50}) Study in Rats with CL-11344/216 EC [Note: Study conducted using OECD Guidelines.]

Test Material: CL-11344/216 EC (45.7% ai; 3.75 EC)

Accession Number: 073307

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co. Ag., Switzerland

RCC Project Number: 039093

Testing Period: November 27 to December 11, 1984

Report Submitted to Sponsor: December 1984

Materials and Methods:

Five male and five female KFM-Han Wistar (outbred SPF-quality) young adult rats (8-10 weeks old) weighing 177 to 233 g were acclimated to laboratory conditions for 7 days prior to treatment. The animals were housed individually in Makrolon type-3 cages and placed in an animal room with controlled temperature, humidity and light. Food and water were available ad libitum.

Approximately, 24 hours before treatment the backs of the animals were shaved exposing an area of approximately 20 cm^2. The test article was applied to the exposed skin at a single dose level of 2000 mg/kg (application volume of 2 mL/kg), and covered with an occlusive dressing which was held in place by an elastic adhesive bandage. The dressing was removed from the skin 24 hours after application and the skin reaction was assessed according to the method of Noaks and Sanderson ("a method for determining the dermal toxicity of pesticides").

Treated animals were observed for signs of toxicity and mortality four times during day 1 and once daily thereafter. Individual body weights were recorded immediately prior to treatment (day 1) and on days 8 and 15 after treatment. Necropsies were performed on all treated animals at the termination of the study.

Results:

Male and female rats treated with the test article survived until termination of the study. All animals, with the exception of one female, gained weight after treatment as recorded on days 8 and 15. Weight loss was recorded for one female rat by day 8 although weight increase was recorded from day 8 to day 15. No

other signs of toxicity were observed in any of the animals. Necropsies performed at sacrifice did not reveal any pathologic changes in male or female rats.

Conclusions:

The AD LD_{50} for CL-11344/216 EC in male and female Wistar rats was determined to be greater than 2000 mg/kg body weight.

Classification: Core-Guideline

Category of Toxicity: III

SUBJECT: Acute Aerosol Inhalation (LC_{50}) Toxicity Study (4-Hour Exposure) with CL-11344/216 EC in Rats [Note: Study conducted using OECD Guidelines.]

Test Material: CL-11344/216 EC (45% ai; 3.75 EC)

Accession Number: 0733307

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co., Ag., Switzerland

RCC Project Number: 039126

Testing Period: November 23 to December 28, 1984

Report Submitted to Sponsor: January, 1985

Materials and Methods:

Male and female KFM-HAN Wistar (outbred, SPF-quality) rats 9 to 12 weeks old and weighing between 186 and 282 g each were acclimated for 7 days under laboratory conditions prior to treatment. The animals were divided into four groups (five male and five female each) and housed in Makrolon type-4 cages (five animals/cage) with food and water available ad libitum. Animal cages were kept in a room with controlled temperature, humidity, and light.

Each group of rats was exposed to one of four test article concentrations (1175, 2033, 3361, or 3767 mg/m^3) for 4 hours. Exposures were conducted in 100-liter polyvinylchloride "nose only" chambers where only the snouts and the nostrils of the animals were exposed to the aerosol. The air flow in the chambers was maintained at 17.5 L/minute. The chamber exposure concentrations were determined gravimetrically at regular intervals throughout the exposure period. Aerosol particle size was determined gravimetrically with the aid of 4-stage cascade impactor (Casella Ltd, London, England) on selectron filters. The temperature, relative humidity, and oxygen content in chamber air were also monitored during exposure.

Treated animals were observed for signs of toxicity and/or mortality four times during the first day and on daily intervals thereafter. Body weights were recorded on day 1 (just prior to exposure) and on days 8, 15 and/or 22 postexposure. All animals that either died during the study or survived to termination of the study were subjected to necropsy.

Results:

The following mortalities were recorded in rats exposed to different concentrations of the test article:

Dose mg/m^3	No. dead M	No. dead F	% Mortality M	% Mortality F	Total No. dead M&F	Total Mortality % M&F
1175	0/5	0/5	0	0	0/10	0
2033	2/5	2/5	40	40	4/10	40
3361	1/5	3/5	20	60	4/10	40
3767	3/5	3/5	60	60	6/10	60

The calculated LC_{50} values (after 22 observation days) were:

Both sexes (M&F) LC_{50} = 3282 mg/m^3
Males LC_{50} = 3832 mg/m^3
Females LC_{50} = 2904 mg/m^3

Particle size distribution analysis revealed that approximately 80 percent of the particles were 10 microns or less.

The mean body weight of animals exposed to the lowest dose (1175 mg/m^3) of test article increased slightly (by 9%) in males and remained the same in females 15 days postexposure (Note: male and female rats exposed to 1175 mg/m^3 were sacrificed on day 15). Mean body weight for animals on the other three higher dose levels was slightly depressed by day 8 post exposure in both sexes, and by day 22 the mean body weights in females were still lower than the corresponding weights on day 1 while in males they were slightly higher. The higher susceptibility of female rats to the toxicity of the test article (as compared to the male rats) might be partly explained by the lower initial body weight of females and hence higher exposure to the test article (as mg/kg). However, a review of the AO LD_{50} data indicated that females were more susceptible than males on a mg/kg basis.

Toxic signs (other than body weight loss) were seen in most animals in all four dose groups and consisted mainly of: sedation, dyspnea, curved body position, emaciation, inspiration noise, ataxia, and ruffled fur. These symptoms were more pronounced in the higher concentration groups (main reason for extending the obervation period to day 22).

Necropsies were performed on all animals in the study (dead or sacrificed) and the findings are listed below:

1. Dose level: 1175 mg/m^3 - nine out of 10 animals did not reveal any pathologic changes; one animal had smaller spleen than usual, reddened intestine and severe meteorism.

2. 2033 mg/m^3 - nine out of 10 animals had pathologic changes consisting mainly of: lung mottled, with dark red areas; severe meteorism stomach/intestine; spleen and liver smaller than usual; kidneys black or pale; adrenals large, reddened; uterus enlarged filled with fluid.

3. 3361 mg/m^3 - five out of 10 animals had pathologic changes including: lung dark-red; foam excretion; stomach/intestine severe meteorism; spleen smaller than usual; adrenals reddened; emaciated.

4. 3767 mg/m^3 - eight out 10 animals exhibited pathologic changes which included: lung dark-red focal, marmorated; stomach/intestine reddish with severe meteorism, filled with reddish contents; small intestines, meteorism, filled with yellow foam.

Conclusions:

The AI LC_{50} for CL-11344/216 EC expressed as gravimetric concentration was determined to be 3282 mg/m^3 in both sexes with 95% confidence limits of 2323-14020 mg/m^3.

Classification: Core-Guideline

Category of Toxicity: III

Subject: Primary Eye Irritation Study with CL-11344/216 EC in Rabbits [Note: Study Conducted Using OECD Guidelines.]

Test Material: CL-11344/216 EC (45% ai;3.75 EC)

Accession Number: 073307

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co. Ag., Switzerland

RCC Project Number: 039104

Testing Period: December 4-7, 1984

Report Submitted To Sponsor: January 1985

Materials and Methods:

Two female and one male New Zealand white rabbit, (Kleintierfarm Madoerin Ag., Switzerland) 14-15 weeks old and weighing 2.4 to 2.7 kg each were acclimated to laboratory conditions for 4 days prior to treatment. The animals were housed individually in stainless steel cages and placed in an animal room with controlled temperature, humidity, and light. Food and water were available ad libitum.

A single dose of undiluted 0.1 mL of test article was administered to the left eye of each animal while the untreated right eyes served as reference controls. The treated and untreated eyes of each animal were examined for irritation at 1, 24, 48, and 72 hours after administration, using the OECD Guidelines for evaluation. Corneal, iridic, and conjunctival irritation were graded using a subjective (basically Draize Scoring System) numerical scoring system. All animals were observed for other toxicity symptoms and mortality. Individual body weights were recorded at day 1, prior to treatment, and at the termination of the study (72 hours posttreatment). No necropsy was performed.

Results:

No acute toxic symptoms or mortality was observed in the treated animals. Eye irritation was observed in all treated animals and consisted mainly of redness, chemosis and severe discharge of the conjunctivae and slight opacity of the cornea in one rabbit which appeared reversible. irritation was observed at 1 hour after treatment with a mean score of 3 out of a possible score of 13. The highest irritation was recorded at 24 hours (mean score of 4), and at 48 hours the mean irritation score was down to 2. By 72 hours eye irritation decreased so

that the mean irritation score was only 0.3 (table 1). The primary mean score in all three animals from 1 hour to 72 hours was 2.3 out of a possible maximum score of 13.

Table 1

CL-11344/216 EC: Eye irritation in Male and Female Rabbits

Animal & Sex	Observation Time[2]	Eye Irritation Scores[1]					
		Corneal Opacity	Iris	Conjunctivae Redness	Conjunctivae Chemosis	Cumulative Score	Mean Score
Male	1 hour	0	0	2	1	3	
Male		0	0	2	1	3	3
Female		0	0	2	1	3	
Male	24 hours	0	0	2	2	4	
Male		1	0	2	1	4	4
Female		1	0	2	1	4	
Male	48 hours	0	0	1	1	2	
Male		1	0	1	0	2	2
Female		1	0	1	0	2	
Male	72 hours	0	0	0	0	0	
Male		1	0	0	0	1	0.3
Female		0	0	0	0	0	

[1] Scoring System - Maximum cornea score 4
iris score 2
redness score 3
chemosis score 4
Maximum cumulative score 13

[2] Treated eyes were not rinsed.

Conclusions:

CL 11344/216 is considered to be a moderate eye irritant. The data indicated diminishing corneal involvement with time and suggested a complete reversibility in 7 days.

Classification:

The present study is classified as core-minimum with OECD guidelines given due consideration.

Category of Toxicity: III

Subject: Primary Dermal Irritation Study with CL-11344/216 EC in Rabbits [Note: Study conducted using OECD Guidelines.]

Test Material: CL-11344/216 EC (45% ai; 3.75 EC)

Accession Number: 073307

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co. Ag., Switzerland

RCC Project Number: 039115

Testing Period: December 4-7, 1984

Report Submitted To Sponsor: January 1985

Materials and Methods:

Two female and one male New Zealand white rabbits, (Kleintierfarm Madoerin Ag., Switzerland) 14-15 weeks old and weighing 2.4 to 2.7 kg each were acclimated to laboratory conditions for 4 days prior to treatment. The animals were housed individually in stainless steel cages equipped with automatic cleaning and drinking system. The animals were kept in a room with controlled temperature, humidity, and light. Food and water were available ad libitum.

Twenty-four hours before treatment the backs of the animals were shaved exposing an area of approximately 100 cm^2. The test article, 0.5 mL, was applied to the intact skin and covered with surgical gauze, aluminum foil, and an occlusive dressing, held in place with an elastic bandage. Four hours after application, the dressing was removed and the treated skin was flushed with lukewarm water. The skin reaction was assessed at 1, 24, 48, and 72 hours after the 4-hour exposure, according to the OECD guidelines. The study was terminated 72 hours after application of the test article. Body weights were recorded on day 1 (prior to exposure) and at termination of the study (72 hours). Observations for toxicity symptoms or mortality were carried out daily. No necropsy was performed at termination.

Results:

All animals survived the treatment of the test article and did not exhibit any overt signs of toxicity during the 72-hour observation period. Skin irritation, in the form of erythema (slight) was observed in all three animals at all observation time points (1, 24, 48, and 72 hours postexposure). Erythema was more pronounced at the early time point (1 hour) and only

slightly visible at later time points. Table 1 shows the irritation scores for individual animals at four observation time points. No edema was observed in any of the treated animals.

TABLE 1

Observation Time (hours)	Animal and Sex	Skin Irritation Scores			
		Erythema	Edema	Cumulative	Mean (N=3
1	Male	2	0	2	
	Female	2	0	2	1.7
	Female	1	0	1	
24	Male	1	0	1	
	Female	2	0	2	1.3
	Female	1	0	1	
48	Male	1	0	1	
	Female	2	0	2	1.3
	Female	1	0	1	
72	Male	1	0	1	
	Female	2	0	2	1.3
	Female	1	0	1	

Conclusions:

CL-11344/216 EC causes slight irritation when applied on the intact skin of New Zealand white rabbits. The primary irritation score was determined to be 1.3 out of a maximum possible score of 8.

Classification:

This study is classified as core-minimum with OECD guidelines given due consideration.

Category of Toxicity: III

Subject: Acute Oral Toxicity (LD_{50}) Study with Lentagran WP in Rats [Study conducted using OECD Guidelines.]

Test Material: Lentagran WP (45% ai)

Accession Number: 073280

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co., AG., Switzerland

RCC Prospect Number: 039137

Testing Period: November 20-December 18, 1984

Report Submitted to Sponsor: December, 1984

Materials and Methods:

Male and female KFM-Han Wistar (outbred, SPF-quality) rats, 8to 10 weeks old, weighing between 160 and 298 g were acclimated under laboratory conditions for 1 week prior to treatment. The animals were housed in Makrolon type-3 cages, 5 per cage, and kept in an animal room with controlled temperature, humidity and light. Food and water were available ad libitum.

The test article was prepared as a suspension (weight by volume) using the vehicle, 2 percent solution of carboxymethylcellulose natriumsalt purum, in distilled water. The preparation was made immediately prior to dosing and its homogeneity during treatment was maintained using a magnetic stirrer. The animals were divided into 4 groups (5 males and 5 females each) and after being fasted for 12 to 18 hours (with free access to water), each group was administered orally one of four test article concentrations (1,000, 2,000, 3,500 and 5,000 mg/kg in a total volume of 10, 10, 20 and 20 mL/kg, respectively).

Treated animals were observed for signs of toxicity and mortality 4 times during test day 1 and daily during days 2 through 15. Individual body weights were recorded on day 1, just prior to dosing, and on days 8 and 15 after dosing. Necropsies were performed on all animals. All surviving animals were anesthetized with sodium pentobarbitdl and killed by exsanguination on day 15. The LD_{50} values were estimated using a LOGIT-model.

Results:

All animals treated with the lowest dose (1000 mg/kg) survived until the end of the observation period. All female animals and 1 male lost some weight from day 8 to day 15 of the observation period. The remainder of the males gained

weight during the same period. Other signs of toxicity in both sexes included slight sedation, dyspnea and ruffled fur and curved body position, all signs being present only between 1 to 5 hours after treatment.

Treatment of rats with 2,000 mg/kg body weight resulted in 1 mortality in male rats and no mortalities in female rats. All (male and female) surviving animals gained weight during the 15-day observation period. Toxicity signs, observed between 1 to 5 hours after treatment, consisted of moderate sedation and ataxia, severe dyspnea, slight ruffled fur (females) and curved body position.

All animals (male and female) with one exception, administered either 3,500 or 5,000 mg/kg body weight of the test article died within 3 hours after treatment. Signs of toxicity included; slight to severe sedation, dyspnea, ataxia and spasms and ventral, latero-abdominal or curved body position.

The LD_{50} values were estimated for each sex or both sexes combined from the following mortality table:

Dose mg/m^3	No. dead M	No. dead F	% Mortality M	% Mortality F	No. dead M&F	% Mortality M&F
1,000	0	0	0	0	0	0
2,000	1	0	20	0	1	10
3,500	5	5	100	100	10	100
5,000	5	5	100	100	10	100

LD_{50} - Males = 2205 (1535 - 4107) mg/kg

Females = 2377 (1622 - 5426) mg/kg

Male & Female = 2330 (1840 - 3379) mg/kg

Gross necropsies were performed on all animals in the study. No pathologic changes were observed in male or female animals that were sacrificied at the end of the study. From the animals that died during the study (11 males and 10 females) only 5 (3 males and 2 females) revealed a pathologic change consisting of yellow discolored colon.

Conclusions:

The $AOLD_{50}$ for Lentagran WP (45% ai) in male and female Wistar rats was estimated to be 2,330 mg/kg with 95 percent confidence limits of 1840-3379 mg/kg.

Classification: Core-Guideline

Category of Toxicity: III

Subject: Acute Dermal Toxicity (LD_{50}) Study with Lentagran WP in Rabbits [Study Conducted Using OECD Guidelines.]

Test Material: Lentagran WP (45% ai)

Accession Number: 073280

Sponsor: Chemie Linz Ag., Austria

Testing Facility: Research and Consulting Co., Ag., Switzerland

RCC Project Number: 036988

Testing Period: November 2-16, 1984

Report Submitted to Sponsor: November, 1984

Materials and Methods:

Five male and 5 female New-Zealand White rabbits (Kleintierfarm Madoerin Ag., Switzerland), 15 to 16 weeks old, weighing between 2.0 and 2.9 kg each were acclimated under laboratory conditions for 1 week prior to treatment. The animals were housed individually in stainless steel cages equipped with automatic cleaning and drinking system, and kept in an animal room with controlled temperature, humidity, and light. Food and water were available ad libitum.

Approximately 24 hours before treatment, the backs of the animals were shaved exposing an area of approximately 40 cm^2. The test article was prepared as a weight/volume dilution using the vehicle, 2% solution of carboxymethylcellulose natriumsalt purum, in distilled water. The preparation was made immediately prior to dosing and its homogeneity during treatment was maintained using a magnetic stirrer. On test day 1 the test article was applied to the exposed skin at a single dose level of 2,000 mg/kg (in a total volume of 4 mL/kg), and covered with an occlusive dressing (wrapped around the abdomen) and held in place by an elastic adhesive bandage. Twenty-four hours after application the dressing was removed, the skin flushed with lukewarm water and the skin reaction was assessed according to the method of Noaks and Sanderson ("a method for determining the dermal toxicity of pesticides").

Treated animals were observed for signs of toxicity and mortality 4 times during test day 1 and daily during days 2 to 15. Individual body weights were recorded on test day 1 (immediately prior to treatment) and on days 8 and 15 after treatment. Necropsies were performed on all treated animals at the termination of the study (day 15).

Results:

All male and female animals exposed to the test article survived until termination of the study. Although the mean body weight of the 5 male and 5 female rabbits increased during the observation period, 2 males and 1 female lost weight during the same period. No other systemic symptoms were observed in any of the animals. Skin irritation, in the form of slight to moderate erythema and/or edema, was observed in all animals from day 2 to day 12 of the observation period.

Necropsies performed at the termination of the study revealed the following pathologic changes in the females: lung, mottled, focal (2); lung mottled, slight (1); lung reddened, marginal area white (1). No pathologic changes were seen in the male rabbits.

Conclusions:

The $ADLC_{50}$ for Lentagran WP in male and female New Zealand White rabbits was determined to be greater than 2,000 mg/kg body weight.

Classification: Core-guideline

Category of Toxicity: III

Note: The percent active ingredient in this formulation was not specified. However, the WP is assumed to contain 45% ai, based upon information provided in the $ADLD_{50}$ study.