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Occupational Toxicological Characteristics of LLM-105 Explosives

Yu Weifei[1], Liao Longyu[1, *], Chen Feilan[2], He Mingzhong[2], Tan Dongmei[2], Fan Guijuan[1], Hao Shilong[1], Lu Huanchang[1]

[1]Laboratory of Energetic Materials, Institute of Chemical Materials, China Academy of Engineering Physics, Mianyang, China

[2]Center of Experimental Animals, Chongqing Medical University, Chongqing, China

Email address:

yuwf_1988@caep.cn (Yu Weifei), 1356412961@qq.com (Liao Longyu)

[*]Corresponding author

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Abstract: LLM-105, a novel nitro-substituted explosive, was evaluated for its occupational toxicological characteristics. Acute oral toxicity tests showed that the maximum tolerated dose should be 8% concentration (gastric irrigation 20mL/kg) and the minimum lethal dose should be 10% (gastric irrigation 20mL/kg). Acute dermal toxicity tests showed that LD50 should be more than 2000 mg/kg. Acute eye irritation tests showed that only slight irritations were found. Skin sensitization tests showed that slight allergic reactions were found. It was suggested that LLM-105 should be generally slightly toxic under normal process which should be positive as preliminary evaluation for occupational protection.

Keywords: 2, 6-diamino-3, 5-dinitropyrazine-l-oxide (LLM-105), Toxicological Evaluations, Occupational Toxicological Characteristics

1. Introduction and Background

Nitro-substituted explosives, such as TNT (2,4,6-trinitrotoluene), RDX (1,3,5-trinitro-1,3,5-triazacyclohexane) and HMX (1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane), were manufactured in thousands of kilograms each year and become the most conventional and widespread explosives in military applications today. Extensive contamination [1-5] and toxicity hazards [6-10] had been seriously concerned from manufacturing, testing and using these explosives for several decades. Toxicities of their derivatives, metabolites, and etc. were also researched though typical derivatives appeared less toxic than the parent compound [11-20]. CL-20 (2,4,6,8,10,12-Hexanitro-2,4,6,8,10,12-Hexaazaisowurtzitane), a nitro- substituted explosive invented later and famous due to its high energy, had also been concerned about its bioconcentration and toxicities translocation [21-25].

LLM-105 (2,6-diamino-3,5-dinitropyrazine-l-oxide), a new nitro-substituted and insensitive high explosive with high melting point [26-29], was not reported about its toxicity hazard yet within the passing decade. Toxicity and pathological changes of LLM -105 were experimented in the context which shall be positive for procedures of manufacturing and application.

2. Materials and Methods

2.1. Materials and Supplies

LLM-105, purity ≥ 98%, manufactured and purified [30-32] in Institute of Chemical Materials, China Academy of Engineering Physics;

DMSO (dimethyl sulphoxide), commercial reagent, from Sigma-Aldrich;

KM mice (Mus musculus), weight of 18 - 22 grams, half male and half female, SPF degree, cultivated in Center of Experimental Animals, Chongqing Medical University, used in acute oral toxicity tests

New Zealand rabbits (Oryctolagus cuniculus), weight about 2000 - 3000 grams, half male and half female, cultivated in Center of Experimental Animals, Chongqing Medical University, used in acute dermal toxicity tests and

acute eye irritation tests.

Healthy adult guinea pigs (Rattus norvegicus), weight about 250 - 300 grams, half male and half female, cultivated in Center of Experimental Animals, Chongqing Medical University, used in skin sensitization tests

2.2. Tests and Methods

Acute oral toxicity tests, according to China standard GBT 21603-2008 and China occupational health standard GBZT 240.2-2011

Acute dermal toxicity test, according to China occupational health standard GBZT 240.3-2011

Acute eye irritation / corrosion test, according to China occupational health standard GBZT 240.5-2011

Skin sensitization test, according to China occupational health standard GBZT 240.7-2011

3. Results and Discussion

3.1. Acute Oral Toxicity

LLM-105 owned considerable solubility in DMSO and LLM-105 - DMSO solution were employed in the pretest. The experimental mice were grouped randomly and dosed 20 ml/kg with gastric irrigation. The mice should be fasting 3 - 4 hours after contamination. As given in Table 1, one mouse showed dispirited, limbs twitch, tremulous, and short of breath at 4 - 6 hours after contamination and got right within observing period. It was eyeable that 12% LLM-105 - DMSO solution induced toxic effects.

Sequent pretests were processed for 12% LLM-105 - DMSO solution and DMSO. The results showed that mice died in DMSO group and solution group. It was assumed that both LLM-105 and DMSO should cause toxic action. In order to avoid the impact of DMSO, the formal tests followed with physiological salt solution as dispersant of LLM-105.

Table 1. *Acute oral toxicity tests and results of LLM-105 - DMSO solution.*

Batch	group	amounts of mice	Activities	pathological changes	Death
Batch first	DMSO	3	without abnormality	-	0
	3% LLM-105 - DMSO solution	3	without abnormality	-	0
	6% LLM-105 - DMSO solution	3	without abnormality	-	0
	12% LLM-105 - DMSO solution	3	abnormal	without definite changes	0
Batch second	DMSO	10	abnormal	without definite changes	1
	12% LLM-105 - DMSO solution	10	abnormal	without definite changes	1

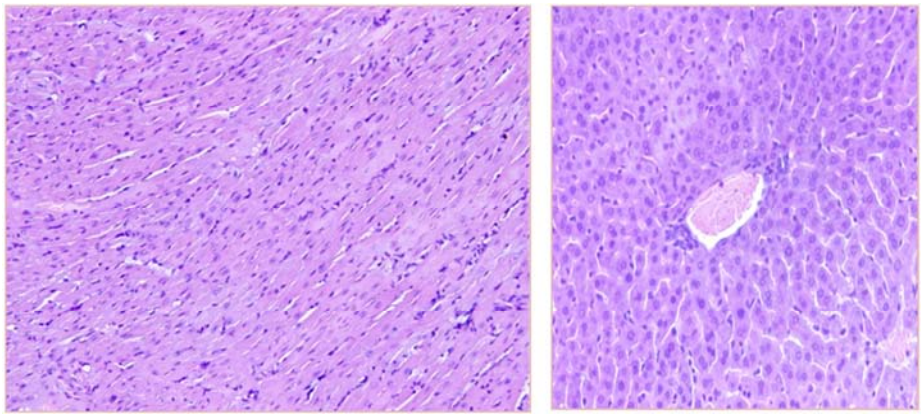
Suspensions of LLM-105 - physiological - salt - solution (12%) were dosed 20 ml/kg with gastric irrigation and the results were given as the batch third in Table 2. One mouse in suspension group defecated dejecta like carbon black 4 - 6 hours after contamination, acted dispirited, showed nigrescent around crissal section after three days, and died after four days. Other mice in comparison group and suspension group showed no abnormity within observing period. Gross anatomy showed no pathological changes.

Formal experiments were processed with suspensions of LLM-105 - physiological-salt-solution. Experimental parameters and results were given as the batch fourth in Table 2. Six mice in 12% group defecated dejecta like carbon black after contamination, one of them died, and five of them returned to normal. Two mice in 10% group died at third day and seventh day respectively. Other mice in comparison group and suspension group showed no abnormity within observing period. The average weight of three experimental groups showed no statistical differences from that of comparison group before and after the test.

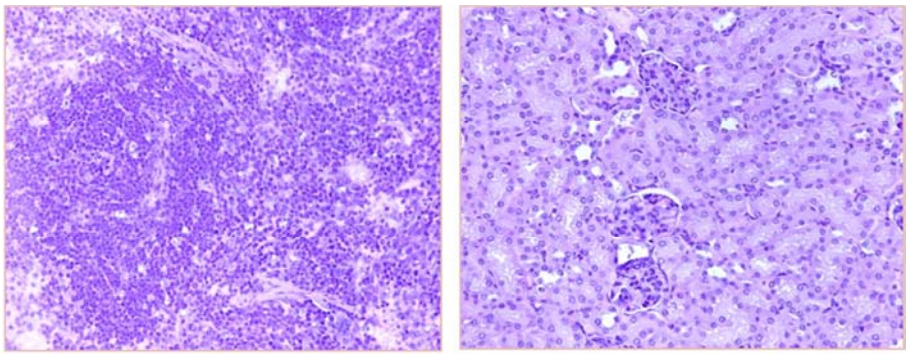
Table 2. *Acute oral toxicity tests and results of LLM-105 - physiological-salt-solution solution.*

Batch	Group	amounts of mice	Activities	pathological changes
Batch third	physiological-salt-solution	6	without abnormality	-
	12% LLM-105 - physiological-salt-solution suspension	6	abnormal	without definite changes
Batch fourth	physiological-salt-solution	10	without abnormality	without definite changes
	8% LLM-105 - physiological-salt-solution suspension	10	without abnormality	without definite changes
	10% LLM-105 - physiological-salt-solution suspension	10	abnormal	slight edema
	12% LLM-105 - physiological-salt-solution suspension	10	abnormal	slight edema

Histopathological change of representative sections from dead mice tissues were observed by hematox-eosin stain and light microscope. As given in Fig. 1, no pathological changes were found except slight edema of central liver veins and circumambient veins.



Cardiac muscle HE×100 Liver HE×150



Spleen HE×100 Kidney HE×100

Fig. 1. *Micrographs of representative sections from dead mice tissues.*

In conclusion, 12% group and 10% group showed a death rate round 10% which suggested that 10% should be minimum lethal dose; 8% group showed a death rate of 0% which suggested 8% should be maximum tolerated dose.

3.2. Acute Dermal Toxicity

Acute toxic action and intensities of LLM-105 due to skin contamination and percutaneous permeation were measured according to Standard GBZT 240.3-2011.

New Zealand rabbits with their weights about 2000 – 3000 grams were prepared according to standard requirements in advance and their skins along dorsal midline were shaved and preserved 24 hours before. Suspensions of LLM -105 - physiological-salt-solution (ratio of 20 grams / 15 milliliter) was prepared as experimental samples and shall be shaken up before application. According to dose 2000 mg/kg, LLM -105 - physiological-salt-solution were weighted up and applied evenly to the preserved skin along dorsal midline of rabbits and covered with sulfuric acid paper and two pieces of gauze. The districts were fixed with bandage or plaster to kept samples in intimate contact to skin and cleaned 24 hours later with tepid water.

The rabbits in LLM-105 group showed no abnormality with 24 hours' coating period. Within observing period, seven showed gentle rubefaction of contaminated skin within 48 - 72 hours and returned to normal after 96 hours, seven reduced their feed-intake and returned to normal after five days, four showed diarrhoea, no other abnormality emerged, and no rabbits died. Gross anatomy showed no definite pathological changes.

The rabbits in comparison group did not show any skin abnormality, toxic action, or death within observing period. Gross anatomy showed no definite pathological changes.

The average weight of the experimental group showed no statistical difference ($P>0.05$) from that of comparison group within observing period.

Table 3. *Acute dermal toxicity tests and results of LLM-105 - physiological-salt-solution solution.*

Batch	group	amounts of mice	Activities	pathological changes	average weight	
					before	after
Batch fifth	Physiological salt solution	10	without abnormality	without definite changes	2105 g	2240 g
	LLM -105 - physiological salt solution	10	abnormal	without definite changes	2005 g	2105 g

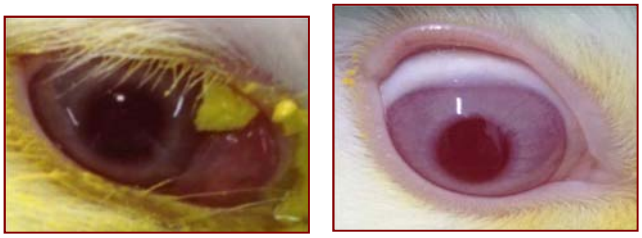
In conclusion, LLM-105 should cause no abnormality except rubefaction, inappetence, and diarrhoea under exposure to maximum dose which suggested that LD50 should be more than 2000 mg/kg.

3.3. Acute Eye Irritation Test

Acute eye irritation actions of LLM-105 were measured according to Standard GBZT 240.5-2011. Three New Zealand rabbits were prepared according to standard requirements in advance.

LLM-105 powder 100 mg was gently put into conjunctival sac of right eye and physiological salt solution 100 ml as comparison was put into that of left eye. The conjunctival sac was cleaned with physiological salt solution twenty-four hours later. Local injuries and irritation were observed carefully and evaluated synthetically according to standard requirements respectively after 1hour, 2 hour, 4 hours, 24 hours, 48 hours, 72 hours, and 96 hours.

The experimental eyes showed conjunctival congestion, vascular bloodshot, edema individually, and ectropium after 1, 2, 3, and 4 hours as given in Fig. 2. After 2 days, weakening of congestion and vanish of conjunctival edema were observed. After 3 days, vanish of congestion were observed. The irritations actions were scored as in Table 4.



After 1 hour After 3 hours

Fig. 2. *Acute eye irritation actions of rabbit.*

Table 4. *Acute eye irritation test and results of LLM-105 / physiological salt solution.*

Batch	group		First day	Second day	Third day	Fourth day
Batch sixth	LLM-105	score	4.0±1.7	2.7±2.3	0.0±0.0	0.0±0.0
		intensity	slight	slight	no	no
	Physiological salt solution	score	0	0	0	0
		intensity	no	no	no	no

The comparison eyes showed no evidential change of cornea, iris, and conjunctiva within the observing period.

Neither experimental eyes nor comparison eyes showed corneal injury under observation by fluorescein-sodium stain and light microscope.

The acute eye irritation actions were scored according to standard requirements and the irritation intensity were evaluated slight within the first day, slight with the second day, non with the third day, and no within the fourth day.

In conclusion, LLM-105 showed slight irritation at conjunctiva within two days, returned to normal three days later, and showed no abnormality at cornea and iris.

3.4. Skin Sensitization Tests

Skin sensitization action and intensity of LLM-105 were tested according to Standard GBZT 240.7-2011.

Healthy adult guinea pigs were grouped randomly to three groups as given in (Table 4) and treated with Buehler tests methods. At induction exposure period, skin area about 30 X 30 mm at left of backside of guinea pig was shaved off 24 hours before, coated by LLM-105 / sterilized distilled water, two pieces of gauze, and one pieces of cellophane in turn, fixed tightly to skin by non-irritative tape, and cleaned entirely six hours later. The process was repeated at seventh day and fourteenth day. At challenge exposure period, skin area about 20 X 20 mm at right of backside of guinea pig was treated with similar process at twenty-eighth day. The skins were observed respectively 24 hours and 48hours after the process. The allergic reaction including Erythema and edema were scored and evaluated synthetically.

Guinea pigs in sterilized distilled water group showed no allergic reaction. Guinea pigs in 1.0g/pig LLM-105 group showed some erythema and scab which was scored and graded. One pig was assessed positive during skin sensitization tests and sensitization rate should be 8.3%. Guinea pigs in 1.5g/pig LLM-105 group showed slight allergic reaction while no pig was confirmed positive. The experiments were repeated and results suggested that guinea pigs in 1.0g/pig LLM-105 group should be more sensitive than that in 1.5g/pig LLM-105 group. The average weight of guinea pigs in experimental groups showed no statistical difference ($P>0.05$) from that in comparison group within observing period.

In conclusion, LLM -105 showed weak allergic reaction to skin of guinea pigs and should be of no skin sensitivity hazard in application.

Table 5. *Skin sensitization tests and results of LLM-105 - physiological-salt-solution solution.*

Batch	group	amounts of mice	allergic reaction	sensitization rate	average weight ($\bar{x}\pm s$)	
					before	After
Batch 7th	0.2ml sterilized distilled water	6	NO	0%	229±5 g	349±11 g
	1.0g LLM-105 /0.2ml sterilized distilled water	12	erythema, scab	8.3%	235±9 g	333±30 g
	1.5g LLM-105 / 0.2ml sterilized distilled water	12	erythema		238±16 g	319±36 g

3.5. Discussion

The nitro-substituted organic explosives were generally reported about their toxicities hazards from using process and their derivatives. Few were literal from their manufacturing process though the toxicities hazards should emerge consequentially from both manufacturing process and using process.

LLM-105 was measured in the context with its toxicological and pathological hazards from manufacturing process. These should be positive to ecotoxicology and environmental safety evaluation of the entire life.

The experiments in the context showed that 8% concentration (gastric irrigation 20mL/kg) should be maximum tolerated dose during acute oral toxicity tests, LD50 should be more than 2000 mg/kg during acute dermal toxicity tests, slight irritation should be determined within acute eye irritation tests, and slight allergic reaction should be determined within skin sensitization tests. The fours tests resulted generally that LLM-105 should be slightly toxic under normal manufacturing process. Such the results should be not reported yet for LLM-105, neither for previous nitro-substituted explosive. It seemed that these test methods typical to chemicals should be unfamiliar to the explosives – one of specialty chemicals and previous nitro-substituted explosive had seldom tested with the methods.

Recent theoretical researches of QSAR (quantitative structure-activity relationships) have been related to acute toxicity prediction [33], insecticidal activity prediction [34], the toxicity of organic analogues to organisms [35], structural modifications of bioactive molecules [36], and etc. Unfortunately, QSAR researches had not aimed at nitro-substituted explosives. It was expectant that explosives should be considerable with their acute toxicities together with their eco-toxicology before extensive release.

4. Conclusions

LLM-105, a new nitro-substituted explosive, was evaluated toxicologically. Acute oral toxicity tests showed 8% concentration (gastric irrigation 20mL/kg) should be maximum tolerated dose. Acute dermal toxicity tests showed that LD50 should be more than 2000 mg/kg. Acute eye irritation tests showed that only slight irritation be found. Skin sensitization tests showed that slight allergic reaction. Though the data could not be compared to their analogues which had seldom tested with the procedure, the fours tests suggested that LLM-105 should be generally slightly toxic under normal manufacturing process which should be positive as preliminary evaluation before application.

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