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TOXICOLOGY EVALUATION OF 2,6,10-TRIAMINO-S-HEPTAZINE

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2,6,10-triamino-s-heptazine (Melem)is a new chemical compound related to the s-triazine family. It is synthesized on the basis of dicyandiamide and is used as a component of several new thermostable polymeric materials. Melem is used in production of distendable fireproofing and coating stable to elevated temperature materials for use in aviation, transportation, construction, wood processing, and other spheres of the national economics.

Physical and chemical properties of Melem are shown in Table 1.

Table 1

Chemical and physical properties of Melem

Chemical formula: $C_6H_6N_{10}$

Molecular mass: 218

Aggregate state: White amorphous dust

Aerosol dispersity:Particles with a size of 2 to 5 microns (81%);

particles 5 to 10 microns (19%)

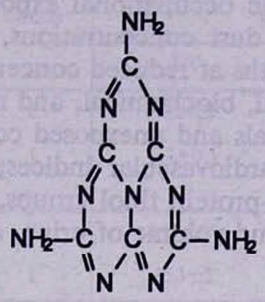
Density: 1.606 *grams/cc*

Solubility: In water, at 25° C, 3 *mg/L*; at 100° C, 600 *mg/L*; in organic solvents, acids, alkalies at room temperature, < 1 to 3 *mg/L*

Reactivity: Non-flammable, non-explosive, melting point >450°C

Purity: Technical grade Melem typically contains 2-4% melamine as an impurity; the permissible level of melamine impurity in the technical material is up to 10% by weight.

Structural formula



Melem is now manufactured in the Republic of Armenia, its production and use are planned to be increased in future. The increased use of Melem will provide numerous opportunities for human contact with this substance.The data concerning the toxicity of Melem are very scarce in literature. There is only one work dealing with the primary evaluation of toxicity of Melem [3]. This, in its turn, requires evaluation of the hazardous properties of Melem and determination of the allowable limit of Melem dust in air of the working zone. Published data concerning the toxicity of Melem and the character and direction of its effect upon the organism is minimal and insufficient to enable scientists to gauge its danger to human health in acute and chronic exposure. Additional data are required to determine the hygienic threshold limit value (TLV) for Melem in production workshops.

Accordingly, our research was carried out to determine the toxicologic character of Melem in the working zone air.

Material and Methods

Toxicologic evaluation of Melem was carried out according to methodologic guidelines and procedures specified by the Ministry of Health of the former USSR [4,11-18,19]. Statistical treatment of the data was carried out using Student's T-test and two-tailed analysis of variance [3-16].

Experimental animals (white mice, white rats, guinea pigs, and rabbits) were subjected to acute and chronic Melem exposures to assess general toxicity to the animal and effects on specific organ systems. Unexposed control animals were used as a basis for comparison with the exposed groups. Toxicologic criteria included external manifestation of intoxication and death, as well as functional, biochemical, and histomorphologic changes in the internal organs.

In acute experiments for each dosage or concentration 8 animals, in subacute experiments – 20, in chronic – 40 animals were exposed. In intact groups the same number of animals was taken.

Melem was administered acutely to experimental animals on the eye and undisturbed skin, orally and intraabdominally as a suspension in vegetable oil,

and by acute and chronic inhalation. Possible transdermal absorption of Melem was assessed toxicologically. Inhalation experiments were performed using inhalation chambers to mimic occupational exposure; single acute inhalation experiments at high Melem dust concentrations, and 4 hours' daily chronic exposures for up to four months at reduced concentrations were conducted.

A wide range of functional, biochemical, and morphologic parameters were assessed in the exposed animals and unexposed controls, including body mass, oxygen consumption, and cardiovascular indices; hemoglobin, glucose, urea, cholesterol, protein and non-protein thiol groups, GOT and GPT enzymes in blood; specific gravity, pH, and volume of urine, and tests of gonadotropic action, among others.

Results and Discussion

Acute Intoxication

The basic toxicometric data obtained for Melem are shown in Table 2.

Table 2

Toxicometric parameters of Melem

Oral DL50 in rats	>5000 *mg/kg*
Oral DL50 in mice	>4000 *mg/kg*
Intraabdominal DL50 in rats	2170±330 *mg/kg*
Intraabdominal DL50 in mice	1998±311 *mg/kg*
Inhalation of dust CL50	>870 *mg/kg*
Limit of acute toxicity	170 *mg/m³*
Limit of chronic toxicity	6 *mg/m³*
Safety Index	3 fold
TLV (from this study)	2 *ml/m³*

Lethality in rats was observed when Melem was introduced orally as a suspension in vegetable oil at doses of 1250 *mg/kg* in rats and higher, with a maximum lethality of 37.5% at a dosage of 5000 *mg/kg*. For mice, initial lethality was observed at 1000 *mg/kg*.

Intraabdominal introduction yielded LD50 of about 2000 *mg/kg* for both mice and rats. Acute single inhalation exposures (Table 3) showed that the threshold of acute toxicity is 170 *mg/m³*, based on changes in oxygen consumption and serum urea concentration. At the maximum concentration tested (870 *mg/m³*), single exposures did not lead to death, but external signs of animal intoxication were observed (reduced mobility, weakness, loss of nutrition reflex, disturbances of respiratory rhythm).

Table 3

Investigations to determine the limit of acute toxicity of a single inhalation of Melem in rats

Index	Group	Concentrations (mg/m^3)		
		870	527	170
Sum. subthreshold electr.impulses (conditional unit)	E	4.7±0.2*	4.1±0.2*	4.4±0.1
	I	5.7±0.1	5.7±0.1	4.0±0.3
Oxygen consumption (*ml/h* 100*gr*)	E	127±6*	142±2*	138±2*
	I	153±2	154±1	155±3
Blood glucose (*mg%*)	E	103±5*	118±8*	88±2
	I	88±3	85±2	87±3
Diuresis (*ml*)	E	5.7±0.3	6.0±0.4	5.9±0.3
	I	6.1±0.4	6.3±0.5	6.3±0.2
Serum Urea (*mg%*)	E	3.5±0.1*	3.6±0.1*	3.7±0.2*
	I	2.4±0.1	2.4±0.2	2.2±0.2

* a statistically significant difference between exposed and control groups; E-experimental group; I-intact group

Effects of Melem following topical application to the eyes and skin were tested. Single applications of Melem did not cause irritation, but suspensions of Melem in water applied to the conjunctive sac of rabbits caused a slight transient redness.

Repeated application to the skin as a paste in lanolin did not cause skin-resorbtive or sensitization effects (Table 4). Melem appeared to have a low order of acute toxicity.

Cumulativity

Cumulativity was studied by daily introduction for 24 days of 420 *mg/kg* (about 1/5 of the intraabdominal LD50) into the stomach of rats [7]. During and after these experiments no deaths were recorded. Thus, Melem appears to have a low order of cumulativity.

Chronic Inhalation Exposures

Chronic inhalation exposure was used to assess the threshold concentration of Melem and effects of the long term exposure on various organs and organ systems.

Table 4

Estimation of the skin resorbtive action of Melem after 10 applications of Melem paste in lanolin to cleaned skin

Index	Group	Rats		Guinea Pigs	
		Before	After	Before	After
Body mass (*grams*)	E	182±4	186±5	326±8	352±7
	I	183±6	196±5	331±11	358±7
SSI (conditional units)	E	4.6±0.3	4.7±0.1	–	–
	I	4.8±0.3	5.1±0.4		
Oxigen Consumption (*ml/h/*100*g*)	E	140±4	4.7±6	–	–
	I	136±3	143±5		
Hemoglobin (*gr %*)	E	15.1±0.1	14.8±0.1	14.6±01	14.5±0.1
	I	14.8±0.2	14.6±0.2	15.1±0.3	14.6±0.1
Leukocytes (1000/*ml*)	E	11.6±0.2	11.5±0.2	9.7±0.3	10.1±0.3
	I	11.8±0.3	11.2±0.2	9.4±0.4	9.7±0.3
Serum Urea (*mg %*)	E	3.86±0.2	3.46±0.2	2.9±0.3	3.1±0.3
	I	3.71±0.3	3.65±0.2	3.2±0.2	3.0±0.2

Two series of 4 months' 4 hours per day exposures were carried out at 32 (high concentration) and 6 mg/m^3 (low concentration). The data obtained in these experiments are summarized in Tables 5-9. Generally, the data presented are for those indices for which toxic effects ascribed to Melem exposure were observed.

The data show significant disturbances after chronic exposure to Melem of 32 mg/m^3. Included is the inhibition of normal increase in body mass and reduced ability to summarize subthreshold electrical impulses. Biochemical indices of blood serum as well as urine are affected; a rise in the frequency of chromosomal alterations in bone marrow cells, morphofunctional effects on the male gonad, and cardiovascular effects are noted.

Data for exposure to Melem of 6 mg/m^3 show fewer changes in the noted indices, and of smaller magnitude, and these effects were generally found to be reversible. Effects on the frequency of chromosomal aberration and male gonad were minimal. Obviously, this concentration of Melem is close to the threshold for chronic action.

Table 5

Physiological and biochemical indices in white rats chronically exposed to Melem at 32 *mg/m³*

Index	Group	After Exposure of			
		30 days	60 days	90 days	120 days
Body Mass	E	212±2*	205±3*	199±3*	200±4*
(*grams*)	I	226±2	236±4	242±3	268±3
SSI	E	3.3±0.1*	3.4±0.1	3.3±0.1*	3.6±0.1
(Conditional units)	I	4.0±0.1	3.7±0.1	3.8±0.1	3.9±0.1
Oxygen Consumption	E	205±9*	197±8*	189±10*	210±9*
(*ml/h* /100 *g*)	I	165±11	156±10	158±10	173±10
Leukocytes	E	11.6±0.3	11.8±0.4	13.5±0.4*	13.0±0.4*
(1000 *ml*)	I	11.3±0.1	11.1±0.4	10.9±0.3	11.3±0.2
Total Protein	E	7.7±0.1*	7.2±0.2*	8.1±0.1	8.5±0.2
(*g %*)	I	8.8±0.2	8.9±0.3	8.8±0.2	8.7±0.3
Serum Urea	E	2.5±0.1*	2.0±0.1*	2.4±0.1*	2.0±0.1*
(*gr %*)	I	3.3±0.2	3.0±0.1	3.2±0.1	3.1±0.1
Serum Choles-	E	81±3*	75±4*	73±7	80±4*
terol (*mg%*)	I	68±4	66±1	67±4	67±3
Blood Glucose	E	81±2	87±7	74±3*	65±4*
(*mg%*)	I	86±4	90±3	88±1	86±2
Nonprotein SH-groups	E	4.1±0.2*	3.5±0.2*	4.4±0.3*	4.9±0.3*
(*mmol /L*)	I	3.3±0.1	2.4±0.2	3.2±0.2	3.2±0.3
Protein SH-groups	E	15.3±0.5	16.4±0.4	12.5±0.8*	14.0±0.3*
(*mmol/L*)	I	16.8±0.9	16.2±0.8	14.8±0.4	15.7±0.3
Thymol test	E	2.0±0.3	2.4±0.5	2.0±0.1*	1.9±0.1*
(*cond. unit*)	I	1.5±0.2	1.6±0.4	1.4±0.1	1.3±0.1
GOT activity	E	0.52±0.03	0.53± 0.01	0.62±0.04*	0.56±0.03
(*mmol/ml/h*)	I	0.53±0.02	0.50±0.02	0.51±0.03	0.51±0.03
GPT activity	E	0.39±0.07	0.40±0.05	0.35±0.03*	0.30±0.04*
(*mmol/ml/h*)	I	0.44±0.08	0.41±0.04	0.44±0.03	0.43±0.04*
Urine pH	E	8.3±0.3*	7.9±0.4	8.0±0.3	8.4±0.5
	I	7.1±0.4	7.3±0.3	7.2±0.3	7.4±0.4
Urine Specific	E	1.012*	1.010*	1.018	1.017
Gravity (*g/cc*)	I	1.017	1.018	1.017	1.018
Typical SD for each group: ± 0.001 to 0.002					
Diuresis	E	5.4±0.6	5.3±03*	4.9±0.2*	5.1±0.4
(*ml*)	I	6.6±0.4	6.8±0.4	6.9±0.4	6.6±0.6

* – a statistically significant difference between exposed and control groups.

Table 6

Physiological and biochemical indices in white rats chronically exposed to Melem at 6 *mg/m³*

Index	Group	After Exposure of			
		30 days	60 days	90 days	120 days
Body Mass	E	217±3	228±3	236±3	245±2
(grams)	I	225±3	236±3	242±3	268±5
SSI (conditional	E	3.4±0.1*	3.2±0.1*	3.6±0.1	3.8±0.1
units)	I	4.0±0.1	3.7±0.1	3.8±0.1	3.8±0.1
Oxygen Consumption	E	223±8*	196±7	170±9	201±16
(ml/h/100g)	I	178±12	186±10	163±11	185±8
Leukocytes	E	11.2±0.4	11.4±0.04	12.9±0.3	12.0±0.4
	I	11.3±0.2	11.5±0.4	12.1±0.2	12.4±0.3
Total Protein	E	8.7±0.1	8.4±0.2	8.4±0.2	8.9±0.2
(g%)	I	8.8±0.2	8.8±0.3	8.8±0.2	8.7±0.2
Serum Urea	E	2.0±0.1*	2.0±0.1*	2.4±0.2	2.4±0.2
(mg%)	I	3.4±0.2	3.1±0.1	3.1±0.1	3.1±0.3
Serum Cholesterol	E	70±9	69±2	58±6	68±3
(mg%)	I	68±5	68±2	67±4	67±4
Serum Glucose	E	84±3	65±4	91±3	79±3
(mg%)	I	86±4	81±5	90±7	87±3
Nonprotein	E	3.7±0.2	3.3±0.2	3.2±0.4	3.5±0.4
(SH-groups, *mmol/l*)	I	3.3±0.1	3.4±0.2	3.2±0.2	3.2±0.3
Protein SH-groups	E	15.7±0.4	16.4±0.5	13.6±0.8	13.7±0.4*
(mmol/l)	I	16.8±0.9	16.2±0.9	14.8±0.4	15.6±03
Thymol test	E	1.7±0.3	1.8±0.1	2.0±0.1	2.1±±0.1
(conditional units)	I	1.4±0.2	1.6±0.4	2.0±0.1	2.0±0.6
GOT activity	E	0.57±0.06	0.51±0.02	0.58±0.09	0.60±0.04
(mmol/ml/h)	I	0.53±0.02	0.50±0.02	0.62±0.03	0.65±0.09

Table 7

Cardiovascular action of Melem after 4 months inhalation exposure

Index	Group	Concentrations	
		32 *mg/m³*	6 *mg/m³*
ECG in second lead	E	0.053±0.002*	0.053±0.001
P-Q interval (*sec*)	I	0.042±0.002	0.048±0.003
QRS (*sec*)	E	0.027±0.001	0.023±0.002
	I	0.026±0.002	0.026±0.002
S-T interval (*sec*)	E	0.021±0.002*	0.028±0.003
	I	0.036±0.002	0.030±0.001
T-P interval (*sec*)	E	0.049±0.010	0.030±0.019
	I	0.033±0.004	0.028±0.006
R-R interval (*sec*)	E	0.180±0.010	0.192±0.021
	I	0.184±0.006	0.170±0.006
P (*mV*)	E	0.09±0.01	0.10±0.01
	I	0.08±0.01	0.09±0.01
R (*mV*)	E	0.54±0.06	0.60±0.10
	I	0.59±0.04	0.60±0.01
S (*mV*)	E	0.15±0.02*	0.20±0.03
	I	0.21±0.02	0.23±0.03
T (*mV*)	E	0.11±0.01	0.11±0.01
	I	0.12±0.01	0.10±0.01
ECG in chest lead, tooth amplitude	E	0.10±0.01*	0.09±0.01
P, (*mV*)	I	0.08±0.01	0.09±0.01
R, (*mV*)	E	0.96±0.11	1.00±0.08
	I	0.88±0.06	0.96±0.08
S, (*mV*)	E	0.15±0.02*	0.25±0.04
	I	0.25±0.02	0.30±0.04
T, (*mV*)	E	0.08±0.01	0.10±0.02
	I	0.09±0.01	0.11±0.01
Integral rheography of vessels	E	27.5±1.0*	24.8±1.0
(blood minute volume, *ml /min*)	I	23.7±1.4	24.2±1.2
Blood stroke volume	E	0.056±0.003*	0.059±0.001
(*ml /min*)	I	0.066±0.002	0.061±0.002
Total peripheral	E	396.4±12.8*	368±14.6
	I	350.3±12.4	362.0±12.8

Table 8

Frequency of chromosomal alteration in bone marrow cells of white rats exposed to Melem aerosol

Groups	Concentrations	
	32 *mg /m³*	6 *mg /m³*
Exposed 60 days	2.00±0.55 %	1.40±0.27%
Exposed 120 days	3.06±0.32%*	1.50±0.30%
Intact	1.74±0.41%	1.69±0.30%

Table 9

Gonadotropic action of Melem after 2,5 monts inhalation exposure

Index	Group	Concentrations	
		32 *mg/m³*	6 *mg/m³*
Testicular weight index (%)	E	0.70±0.01*	0.96±0.06
	I	1.03±0.04	1.03±0.04
Osmotic Resistence of	E	3.53±0.019*	4.40±0.23
Spermatozoa (%)	I	4.90±0.10	4.90±0.10
Spermatozoa	E	165.3±22.6*	207.5±11.3
Mobility time *(min)*	I	215.6±12.4	215.6±12.4
Number of Dead	E	42.5±1.3*	22.0±0.8
Spermatozoa (%)	I	20.3±1.3	20.3±1.0

The lower limit threshold concentration of chronic action for Melem was found to be 6 *mg/m³*. Taking into account that Melem has relatively low toxicity, and low cumulativity not associated with the development of long-term effects, a minimal safety factor of three fold is suggested. In December 1994, based on the data obtained by the Armenian research team, the Government Committee of Hygienic Standardization of the Russian Federation promulgated a TLV of 2 *mg/m³* for Melem. In our opinion, the TLV of 2*mg/m³* will assure adequate safety for Melem worker.

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Է.Ա.Բաբայան, Ռ.Դ.Հովհաննիսյան, Ս.Բ.Բաղրամյան, Ա.Վ.Ալեքսանդրյան, Վ.Վ.Գաբուչյան, Պ.Հ.Բակալյան, Վ.Ս.Մադոյան, Լ.Ա.Սարյան

Լաբորատոր կենդանիների վրա դրված սուր, ենթասուր եւ խրոնիկական փորձերում ուսումնասիրվել են 2,6,10-տրիամինո-s-հեպտազինի (մելեմի) թունավոր հատկությունները: Ստամոքս-աղիքային ճանապարհով առնետների եւ մկների օրգանիզմ ներմուծելու դեպքում մելեմը իրեն դրսեւորել է որպես քիչ թունավոր նյութ: Ներորովայնային ճանապարհով ներմուծելիս սահմանվել են միջին մահացու հետեւյալ դոզաները՝ մկների համար 1998±212 *մգ/կգ*, առնետների համար 2170±330 *մգ/կգ*: Շնչառական ճանապարհով 4 ժամ տեւողությամբ միանվագ ազդելու դեպքում առնետների մոտ մահացու ելքեր չեն առաջացել 113-ից մինչեւ 870 *մգ/մ*^{3} խտություններից, իսկ սուր ազդեցության շեմքը գտնվել է 170 *մգ/մ*^{3} մակարդակի վրա:

Մելեմի օրգանիզմում կուտակվելու հատկությունները թույլ են արտահայտված; 4 ամսվա ընթացքում, օրեկան 4 ժամ տեւողությամբ շնչառական ճանապարհով ազդելու դեպքում մելեմի 32±1,1 *մգ/մ*^{3} խտությունը սպիտակ առնետների մոտ առաջացրել է օրգանիզմի ընդհանուր թունավորում, որը դրսեւորվում է կենտրոնական նյարդային եւ սիրտանոթային համակարգերի, շնչառական օրգանների, լյարդի եւ երիկամների կողմից ֆունկցիոնալ եւ հյուսվածաախտաբանական փոփոխություններով: Այդ խտությունը առաջացրել է նաեւ առնետների արական վերարտադրողական ֆունկցիայի խանգարում:

6,0±0,5 *մգ/մ*^{3} խտության ազդեցությունը առաջացրել է քիչ տարածված եւ թույլ արտահայտված անցողիկ բնույթի փոփոխություններ, որոնք գնահատվել են որպես շեմքային: Հիմնավորվել է աշխատանքային գոտու օդում 2,6,10-տրիամինո-s-հեպտազինի սահմանային թույլատրելի խտությունը՝ 2 *մգ/մ*^{3}:

ТОКСИКОЛОГИЧЕСКАЯ ОЦЕНКА 2,6,10-ТРИАМИНО-S-ГЕПТАЗИНА

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В острых, подострых и хронических опытах на лабораторных животных изучены токсические свойства 2,6,10-триамино-s-гептазина (мелем). При введении в желудок мелем проявил себя как малотоксичное вещество. При внутрибрюшинном введении установлены следующие среднесмертельные дозы: для мышей – 1998±212 *мг/кг*, для крыс – 2170±330*мг/кг*. При однократной ингаляционной затравке концентрациями от 113 до 870 *мг/м*^{3} в течение 4 часов смертельных исходов не отмечалось. Пороговой при остром ингаляционном воздействии оказалась концентрация 170 *мг/м*^{3}. Кумулятивные свойства мелема слабо выражены. При 4-месячной ежедневно по 4 часа ингаляционной затравке белых крыс в концентрации 32±1,1 *мг/м*^{3} развивается общая интоксикация организма, которая проявлялась функциональными и патоморфологическими нарушениями со стороны ЦНС, ССС, дыхательных органов, печени и почек. Эта концентрация вызвала также нарушения со стороны мужской репродуктивной функции крыс.

Концентрация 6,0±0,5 *мг/м*³ вызвала лишь маловыраженные и нераспространенные проходящие изменения, которые были расценены как пороговые. Обоснована ПДК 2,6,10-триамино-s-гептазина в воздухе рабочей зоны на уровне 2 *мг/м*³ (аэрозоль, III класс опасности).

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