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SENSORY IRRITATING PROPERTIES OF CYANURIC CHLORIDE AS REVEALED WITH PLETHYSMOGRAPHIC METHOD

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Abstract. Sensory respiratory irritation properties of cyanuric chloride (2, 4, 6-trichlorotriazine; CC) were studied in mice. For this purpose, the respiratory rate was measured in Balb/C male mice by means of the whole body plethysmographic method. Each animal was placed in a body plethysmograph attached to a small (0.25 m^3) dynamic inhalation chamber and exposed to various concentrations (2.1, 6.7, 9.1, 11.7 and 14.6 mg/m^3) of CC. Respiratory rates were recorded before, during and after termination of the exposure.

It was found that exposure to CC caused a concentration-dependant decrease of respiratory rates in mice. After termination of exposure fast and full recovery of respiratory rates were observed within 5 minutes. RD_{50} value calculated with probit method was established as 5.9 (1.3–13.9 for 95% confidence limits) mg/m^3. The slope of the dose response curve was 1.366 (0.78).

It is concluded that cyanuric chloride is a strong respiratory irritant.

INTRODUCTION

Cyanuric chloride (2, 4, 6-trichlorotriazine; CAS No. 108–77–0) is a white powder with pungent odour at room temperature and pressure. It is only slightly soluble in water, but soluble in organic solvents e.g acetone, toluene, chloroform etc. It is used primarily as a chemical intermediate in the production of herbicides, dyes, optical brighteners, pharmaceuticals and plastics.

No workplace standards have been established for this compound.

Cyanuric chloride is used almost exclusively as a process intermediate in closed systems; however, dermal contact and inhalation of the vapour and dust might occur. In the literature there is a paucity of toxicity data on CC, but some of them indicate that CC is a lacrimator and respiratory irritant (11).

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A good correlation was observed between the atmospheric concentration of respiratory irritants at which a 50% decrease of the respiratory frequency in laboratory animals can be observed (RD_{50}) and the threshold limit values for the working place. The RD_{50} might be determined in so-called "Alarie test" (1 – 3). This test is preferably carried out in mice.

The objective of this study was to determine the RD_{50} to set emergency exposure limits for discomfort symptoms and to set occupational exposure limits.

MATERIALS AND METHODS

The respiratory rate was measured in Balb/C male mice, by means of the whole body plethysmographic method. Each animal was placed in a body plethysmograph attached to a small (0.25 m^3) dynamic inhalation chamber and exposed to various concentrations (2.1, 6.7, 9.1, 11.7 and 14.6 mg/m^3) of CC. Ten animals were exposed in each group. Respiratory rates were recorded 10 minutes before exposure, during 15 minutes of exposure and 5 minutes after termination of exposure.

Test material was generated into each exposure chamber as a vapour by letting a geldried air through Libig condenser containing inside the solid CC protected of silanetreated głass wool from both sides. Outer part of the condenser contained circulated water heated to 60–90°C, depending on the concentration to be generated. CC-laden air passed from the condenser exit port, mixed with dried and heated clean air, and then through glass tubing covered with flexible electric heating tapes to the chamber turret.

All the measurements described were taken directly through the sampling port from the test atmosphere feed tube on the flow-past exposure system which delivered fresh test article to the animal's nose. Thus, all sampling represented exactly what was delivered to the animal's nose.

Cyanuride chloride concentrations were determined using gas chromatograpy.

Schematic of generation and exposure system is shown on Fig. 1.

The RD_{50}, the concentration inducing a 50% decrease in the respiratory rate was calculated with probit method using RD_{50} software (8).

RESULTS

It was found that exposure to CC caused concetration-dependant decrease of respiratory rates in Balb/C mice. The maximum decrease of respiratory rate was observed within first 2 minutes of exposure. The plateau for all concentrations was reached in 8 minutes of exposure. After termination of exposure fast i.e. within 5 minutes, and full recovery of respiratory rates were observed. RD_{50} value calculated with probit method was established as 5.9 (1.3 – 13.9 for 95% confidence limits) mg/m^3. The slope of the dose response curve was 1.366 (0.78).

Results, expressed as a % of decrease of respiratory rate as compared to respiratory rate, 1 minute before the start of exposure to CC, are shown in Table 1 and Fig. 2.

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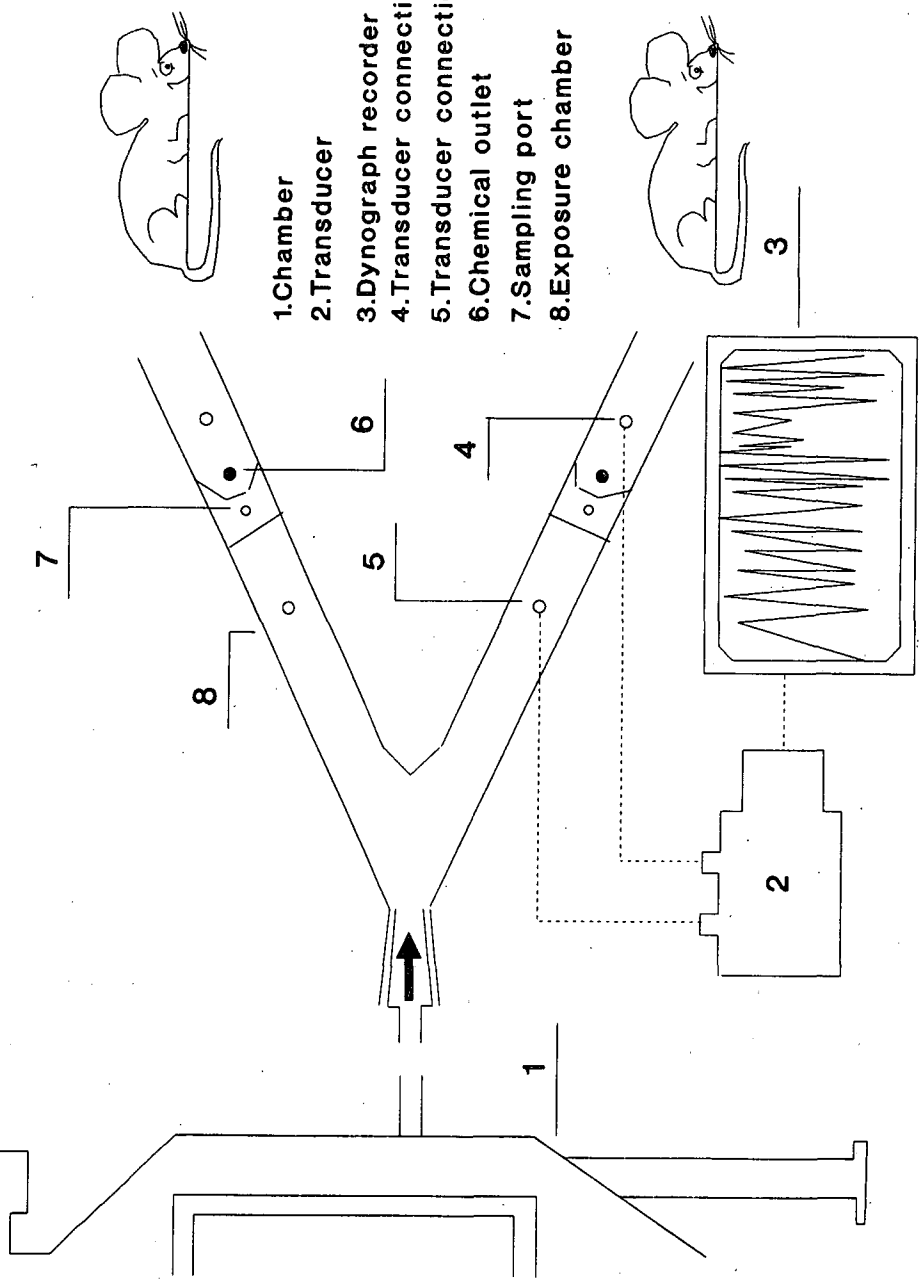

Fig. 1. Schematic of generation and exposure asystem used.

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Table 1. Data on respiratory rates of rats exposed to cyanuric chloride

	2.1			6.8			9.3			11.7			14.6		
	2.07 + 0.12			6.78 + 0.55			9.27 + 0.5			11.72 + 0.39			14.55 + 0.25		
	t	A	B	t	A	B	t	A	B	t	A	B	t	A	B
	1	7	93	1	15	85	1	14	86	1	20	80	1	39	61
	2	8	94	2	35	65	2	39	61	2	46	54	2	50	50
	3	13	87	3	36	64	3	46	54	3	50	50	3	59	41
	4	14	86	4	40	60	4	48	52	4	50	50	4	69	31
	5	21	79	5	43	57	5	48	52	5	53	47	5	70	30
	6	28	72	6	43	57	6	55	45	6	56	44	6	74	26
	7	26	74	7	43	57	7	55	45	7	62	38	7	74	26
	8	26	74	8	47	53	8	56	44	8	66	34	8	74	26
	9	32	68	9	48	52	9	60	40	9	69	31	9	76	24
	10	30	70	10	49	51	10	58	42	10	67	33	10	75	25
	11	32	68	11	52	48	11	59	41	11	64	36	11	76	24
	12	38	62	12	56	44	12	60	40	12	67	33	12	75	25
	13	33	67	13	57	43	13	59	41	13	75	25	13	75	25
	14	30	70	14	56	44	14	61	39	14	68	32	14	74	26
Cease of exposure →	15	34	66	15	54	46	15	59	41	15	66	34	15	72	28
	16	20	80	16	47	53	16	52	48	16	56	44	16	60	40
	17	6	94	17	28	72	17	44	66	17	42	58	17	51	49
	18	7	93	18	20	80	18	22	78	18	30	70	18	42	68
	19	5	95	19	19	81	19	16	84	19	25	75	19	27	73
	20	3	97	20	17	83	20	13	87	20	21	79	20	24	76
	AVG. 31.9			AVG 52.4			AVG 59			AVG 67.7			AVG 74.6		
	STD 3.3			STD 3.7			STD 1.4			STD 3.1			STD 1.2		

t – time of exposure in minutes
A – decrease of respiratory rates exposed/controls in %
B – respiratory rates as percentage of controls

DISCUSSION

It was shown, that inhalation exposure of mice to cyanuric chloride caused marked decrease of their respiratory rates. The RD_{50} of 5.9 mg/m^3 (0.8 ppm) was calculated.

It is known that cyanuric chloride at temperatures above O°C hydrolyzes to cyanuric acid and hydrogen chloride (7). The question arises whether the response observed is caused by the compound itself or by products of their hydrolysis. The sensory irritating effects of hydrogen chloride were determined in mice and RD_{50} calculated as 309 ppm (5). This value is much higher than established in our study for cyanuric chloride. Sensory irritating effects of cyanuric acid were not studied according to the available literature, but irritating properties of this compound are generally much lower than that for cyanuric chloride (7, 12). It means that observed effects are due to the cyanuric chloride itself.

Our results show that cyanuric chloride is a very potent respiratory irritant. It is suggested that sensory irritation can occur due to activation of so called "the sensory irritant receptor" (1, 9, 10). Activation of the receptor can be only due to physical adsorption of the agonist or physical adsorption and chemical reaction with different binding sites of the receptor. The latter is more efficient and this type of reaction

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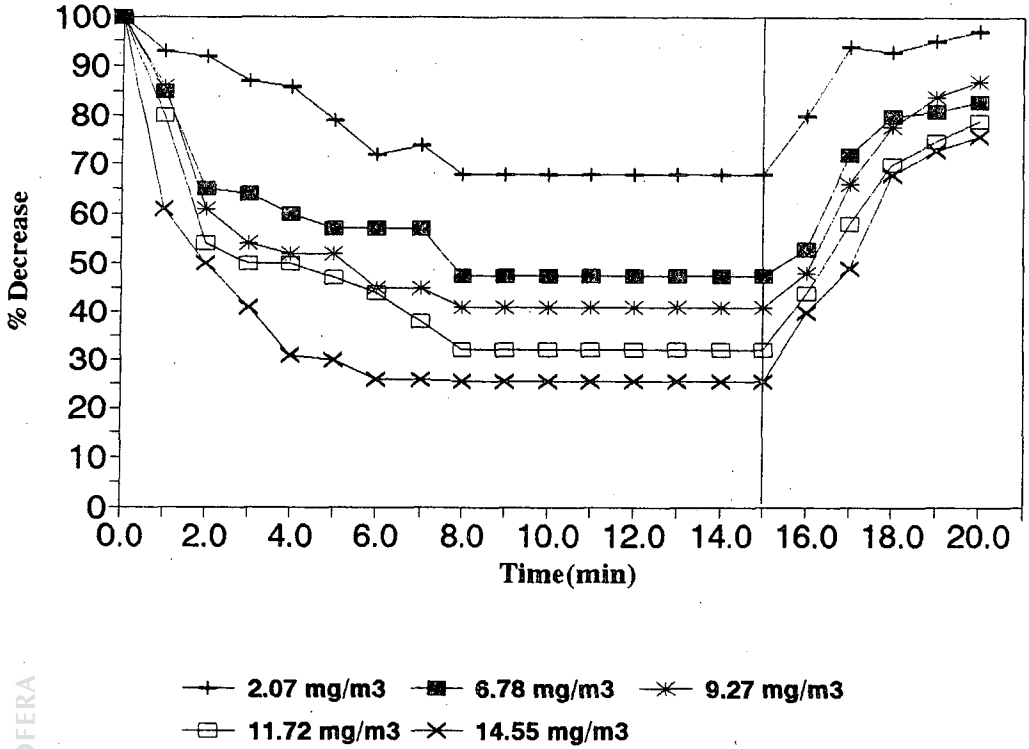

Fig.2. Time-response relationship for the effect of cyanuric chloride in mice. Each point represents the average of 7–10 mice. After termination of exposure (at 15 minutes) fast and full recovery of respiratory rates was observed.

is characteristic for more potent irritants. A model for the receptor protein has been proposed with two main binding sites: for benzene moieties and thiol group (2, 3, 8). In the available literature there are no data on RD_{50} value for triazine compounds. However, the structural similarity of triazine ring and benzene ring is giving rise to optimal binding of this substance. Additionally, it was shown that chlorine can oxidize thiol groups and that presence of the C-Cl group increases the irritating potency of the compound by reaction with a thiol group in the receptor (6, 11). However, the existence of another type of receptor, specific for triazine compounds, should not been excluded.

Barrow et al. (5) proposed that an Occupational Exposure Limit (OEL) , based on prevention of sensory irritation, should be between 0.01 $*RD_{50}$ and 0.1 $*RD_{50}$. Few years later, Alarie (4) argued that a better way of predicting an OEL from the test system was to take a single value instead of a range. The factor of 0.03 RD_{50} was proposed as the highest level acceptable for an OEL, unless other toxic effects occur in the respiratory system at exposure concentrations lower than those at which sensory irritation occurs. He reported that a good correlation (correlation coefficient: 0.92) existed between the logarithm of RD_{50} and the logarithm of the ACGIH TLV of 40 chemicals. This is not surprising since it has been estimated that 60–70% of the TLV values and of the OSHA Toxic Substances list are based on irritation,

mostly sensory irritation. Taking into consideration this assumption the OEL for cyanuride chloride, as based on RD_{50} value should be around 0.17 mg/m^3. However, it is true only when no toxic effects, namely histopathological changes in nasal passages, are found in short-term exposure at or below the RD_{50} (4, 6). Therefore, data from the sensory irritation test will be used to determine the highest exposure concentration in further inhalation toxicity testing.

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