Defence Science Journal, Vol. 59, No. 5, September 2009, pp. 512-516

Prophylactic Efficacy of Amifostine, DRDE-07, and their Analogues against Percutaneously Administered Nitrogen Mustards and Sulphur Mustard

Manoj Sharma*, R. Vijayaraghavan**,Uma Pathak**, and K. Ganesan**

*Shri RNS institute of Pharmaceutical Sciences and Technology, Gwalior
**Defence Research and Development Establishment, Gwalior – 474 002

ABSTRACT

Nitrogen mustards (HN-1, HN-2 and HN-3) and sulphur mustard are alkylating and blister-inducing chemical warfare agents. This study was aimed at investigating the prophylactic efficacy of amifostine, DRDE-07, and their analogues and some recommended antidotes against dermally-applied nitrogen mustards and sulphur mustard in preventing their systemic toxicity in mice. The antidotes were administered as single oral dose, 30 min prior to the mustard agent application. For DRDE-07, 0.2 LD_{50} (249 mg/kg) was used and for other analogues, equimolar dose of DRDE-07 was used. For amifostine, N-acetyl cysteine, melatonin and sodium thiosulphate, oral dose was 185 mg/kg, 250 mg/kg, 250 mg/kg, and 1000 mg/kg respectively. The animals were observed for mortality for 14 days. The protection index (PI) was calculated as a ratio of LD_{50} with treatment to LD_{50} without treatment. The protection of the antidotes was also determined by intraperitoneal route and half of the oral dose of the antidotes was given. The estimated percutaneous LD_{50} of HN-1, HN-2, HN-3 and sulphur mustard was 11.9 mg/kg, 20.0 mg/kg, 7.1 mg/kg and 7.1 mg/kg, respectively.

Compounds that showed marginal protection against HN-1 were DRDE-10 and melatonin with a PI of 1.4. Compounds that showed marginal protection against HN-2 were amifostine, DRDE-07, DRDE-09, DRDE-30, DRDE-35 and melatonin with a PI of 1.4. Compounds that showed marginal protection against HN-3 were amifostine, DRDE-30, DRDE-35, sodium thiosulphate and melatonin with a PI of 1.7. In the case of sulphur mustard, DRDE-07, DRDE-10, DRDE-21, DRDE-30, and DRDE-35 gave a good protection with a PI of more than 5.0. Amifostine and sodium thiosulphate gave a PI of 4.5 and 4.0, respectively, while DRDE-09, N-acetyl cysteine and melatonin gave less protection against sulphur mustard. Intraperitoneally administered amifostine, DRDE-30, sodium thiosulphate and melatonin gave marginal protection against HN-2 with a PI of 1.2, while intraperitoneally administered amifostine, DRDE-07, DRDE-09, DRDE-10, DRDE-30, DRDE-35 and melatonin gave excellent protection against percutaneously administered sulphur mustard with a PI of more than 5.0. The present study shows, that oral and intraperitoneal administration of amifostine, DRDE-07 and their analogues are effective as prophylactic agents for sulphur mustard systemic toxicity, but not against nitrogen mustards.

Keywords: Nitrogen mustards, mechlorethamine, sulphur mustard, acute toxicity, amifostine, DRDE-07, prophylactic efficacy, chemical warfare agents, antidotes

1. INTRODUCTION

Chemical warfare remains a serious threat despite several international conventions and treaties signed to prevent its use. The nitrogen mustards are closely related chemically and toxicologically to the blister-inducing chemical warfare agent sulphur mustard [1]. The nitrogen mustards, viz., HN-1, HN-2, and HN-3 were synthesised during World War I. HN-2, also known as mechlorethamine, was found to be useful for the treatment of various types of malignancies such as Hodgkin's disease, lymphoma, and carcinoma of solid tumors [2]. Few more nitrogen mustards are still used as cytostatic agents, viz., melphalan, chlorambucil and cyclophosphamide [3]. Nitrogen mustards and sulphur mustard become biologically active after their intramolecular cyclisation into immonium ions, aziridinium ions, or sulphonium cations. All these mustards covalently bind to target molecules via an alkylating reaction and produce a variety of toxic effects [4]. DNA is probably the most important target of alkylation by nitrogen mustards.

At present, there are two main strategies to prevent nitrogen mustards and sulphur mustard toxicity. First is contact avoidance and the second is symptomatic treatment, as there are no specific antidotes available to treat the systemic toxicity. For the past two decades, a substantial research effort for developing pharmacological intervention strategies have been focused on *in vitro* studies aimed at preventing or reversing the ability of sulphur mustard to alkylate critical cell targets, disrupt calcium regulation, cause cell death or cause other cell-mediated biochemical disruptions [5,6]. Few compounds have shown good prophylactic as well as therapeutic protection *in vitro* [7,8] as well as *in vivo* against sulphur mustard [9-11]. Some drugs and chemicals have been reported to give protection against sulphur and nitrogen mustards viz., N-acetyl cysteine, sodium thiosulphate, vitamin E [12-14] Sodium thiosulphate has been recommended for the treatment

Received 13 February 2009, Revised 16 July 2009

of human poisoning by mustard gases [15,16]. Amifostine and DRDE-07 [S-2 (2-aminoethylamino) ethyl phenyl sulphide] have been shown to protect sulphur mustard toxicity as a prophylactic agent [10,17,18]. This led researchers at DRDE to study amifostine, DRDE-07, and their analogues for the protection against nitrogen mustard systemic toxicity.

2. MATERIALS AND METHODS

2.1 Chemicals Used

Nitrogen mustards [HN-1, bis-(2-chloroethyl)ethylamine; HN-2, mechlorethamine, bis-(2-chloroethyl)methylamine; HN-3, tris-(2-chloroethyl)amine] and sulphur mustard (2,2-dichloroethyl sulphide) were synthesised in the DRDE and was found to be more than 99 per cent pure by gas chromatographic analysis. Amifostine, DRDE-07 and their analogues were also synthesised in DRDE and were found to be 99 per cent pure by thin layer chromatography. N-acetyl cysteine (NAC) and melatonin were purchased from M/s Sigma Chemical Company (USA). Sodium thiosulphate and other chemicals of high purity were from M/s Qualigens (India) and M/s E-Merck (India).

2.2 Animals Treated

Randomly bred Swiss female mice (25-30 g) from the institute's animal facility were used for the study. The animals were kept in polypropylene cages with sterilised and dry paddy husk as a bedding material. Free access to food and water was allowed until two hours before the experiment. The care and maintenance of the animals were taken as per the approved guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. A day before percutaneous administration of the mustard agents, hair on the back of the animals were closely clipped using a pair of scissors. Food and water were allowed two hours after the experiment. All animal procedures were approved by the institutional Animal Ethical Committee.

2.3 LD_{50} Determination

The analogues of DRDE-07, amifostine, N-acetyl cysteine, and sodium thiosulphate were dissolved in distilled water, and melatonin was dissolved in DMSO. The LD_{50} was determined through oral, and intraperitoneal routes. LD_{50} of nitrogen mustards (diluted in DMSO) and sulphur mustard (diluted in PEG-300) were determined by exposing the animals to increasing doses of mustard agents through percutaneous route of administration. The diluted solution was smeared uniformly on the back of the animals on a circular area of 1.5 cm diameter, using a gas-tight syringe (Harvard Apparatus, USA). The body weight was recorded daily and the animals were observed for mortality for 14 days. LD_{50} was determined as per the moving average method [19].

2.4 Protective Efficacy of Analogues

Amifostine, DRDE-07, and their analogues and other antidotes were administered orally 30 min prior to mustard agent administration by percutaneous route. For amifostine, N-acetyl cysteine, melatonin and sodium thiosulphate, 185 mg/kg, 250 mg/kg, 250 mg/kg, and 1000 mg/kg, respectively was used. For DRDE-07, 249 mg/kg, and for other analogues, equimolar dose of DRDE-07 was used [20]. Animals in the 'toxicant only groups' received distilled water as a pretreatment and then exposed to mustard agents whereas PEG/DMSO was applied on the back of animals in the control group. Body weight of animals was recorded for 14 days and animals were monitored for mortality and general health. LD_{50} of mustard agents after pretreatment were then calculated by exposing the animals to increasing doses of mustard agents. Protective index (PI) was determined as a ratio of LD_{50} of mustard agent after pretreatment to LD_{50} of mustard agent without pretreatment. Another experiment was also performed in which the antidotes were administered intraperitoneally, 30 min prior to mustard agents (HN-1, HN-2, HN-3 and sulphur mustard) administration and PI was determined. For intraperitoneal route, half of the oral dose of the antidotes was given.

3. RESULTS

Table 1 shows the LD_{50} values of the various analogues following oral and intraperitoneal routes in mice. All deaths occurred within 1h to 6 h and no delayed death was observed. The animals appeared normal after 24 h. Table 2, summarises the prophylactic efficacy of various antidotes against percutaneously administered HN-1, HN-2, HN-3 and sulphur mustard. Compounds that showed marginal protection against HN-1 were DRDE-10 and melatonin with a PI of 1.4. Compounds that showed marginal protection against HN-2 were amifostine, DRDE-07, DRDE-09, DRDE-30, DRDE-35, and melatonin with a PI of 1.4. Compounds that showed marginal protection against HN-3 were amifostine, DRDE-30, DRDE-35, sodium thiosulphate and melatonin with a PI of 1.7. In case of sulphur mustard, DRDE-07, DRDE-10, DRDE-21, DRDE-30, and DRDE-35 gave a good protection with a PI of more than 5.0. Amifostine and sodium thiosulphate gave a protection of 4.5 and 4.0, respectively, while DRDE-09, N-acetyl cysteine and melatonin gave less protection against sulphur mustard.

Table 3, summarises the prophylactic efficacy of intraperitoneally administered antidotes against percutaneously administered HN-2 and sulphur mustard. Intraperitoneally administered amifostine, DRDE-30, sodium thiosulphate and melatonin gave marginal protection against HN-2 with a PI of 1.2. Intraperitoneally administered amifostine, DRDE-07, DRDE-09, DRDE-10, DRDE-30, DRDE-35 and melatonin gave excellent protection against percutaneously administered sulphur mustard with a PI of more than 5.0.

4. DISCUSSION

Based on the LD_{50} determination, all the antidotes showed more toxicity by the intraperitoneal route, except sodium thiosulphate. Amifostine and DRDE-07 are already reported as antidotes against the toxic effect of suphur mustard [10,18,21,22]. In this study also a similar result was observed that DRDE-07 is better than amifostine against

Table 1. LD_{50} values of amifostine, DRDE-07 and their analogues and other antidotes in female mice by oral and intraperitoneal routes of administration

Chemicals/ Drugs	Oral LD_{50} (mg/kg)	Fiducial limits (mg/kg)	I.P. LD_{50} (mg/kg)	Fiducial limits (mg/kg)
DRDE - 07	1247	793 - 1962	283	200 - 400
DRDE - 09	1131	800 - 1600	283	200 - 400
DRDE - 10	1902	1245 - 2907	283	200 - 400
DRDE - 21	1131	597 - 2146	283	200 - 400
DRDE - 30	4524	3200 - 6400	673	455 - 996
DRDE - 35	2262	1600 - 3200	336	228 - 498
Amifostine	1049	709 - 1552	951	622-1453
N-acetyl cysteine	> 5000	-	336	228 - 498
Melatonin	1345	909 - 1991	566	400 - 800
Sodium thiosulphate	> 5000	-	> 5000	-

Table 2. Protective effect of various antidotes (oral administration) against percutaneously administered HN-1, HN-2, HN-3 and sulphur mustard in mice

Chemicals/ Drugs	Oral Dose*	LD_{50} of HN-1	PI	LD_{50} of HN-2	PI	LD_{50} of HN-3	PI	LD_{50} of SM	PI
Agent only	-	11.9 (7.8-18.2)	-	20.0 (12.7-31.5)	-	7.1 (3.2-15.7)	-	7.1 (5.0-10.0)	-
+ DRDE-07	249	14.2 (10.0-20.0)	1.2	28.3 (20.0-40.0)	1.4	10.0 (6.1-16.3)	1.4	80.6 (50.0-125.8)	11.4
+ DRDE-09	273	14.2 (10.0-20.0)	1.2	28.3 (20.0-40.0)	1.4	7.1 (5.0-10.0)	1.0	20.0 (12.3-32.6)	2.8
+ DRDE-10	261	16.8 (11.4-24.9)	1.4	23.3 (16.1-35.2)	1.2	11.2 (6.2-20.4)	1.6	56.6 (29.8-107.3)	8.0
+ DRDE-21	254	14.2 (10.0-20.0)	1.2	20.0 (12.7-31.5)	1.0	10.0 (6.1-16.3)	1.4	50.4 (22.6-114.1)	7.1
+ DRDE-30	219	14.2 (10.0-20.0)	1.2	28.3 (20.0-40.0)	1.4	11.9 (7.8-18.2)	1.7	44.9 (21.1-95.4)	6.4
+ DRDE-35	230	14.2 (6.4-31.5)	1.2	28.3 (20.0-40.0)	1.4	11.9 (7.8-18.2)	1.7	50.4 (22.3-114.1)	7.1
+ Amifostine	185	14.2 (10.0-20.0)	1.2	28.3 (16.3-49.3)	1.4	11.9 (7.8-18.2)	1.7	31.8 (12.6-79.8)	4.5
+ N-acetyl cysteine	250	14.2 (6.4-31.5)	1.2	20.0 (12.7-31.5)	1.0	10.0 (6.1-16.3)	1.4	16.8 (11.0-25.7)	2.4
+ Melatonin	250	16.8 (11.4-24.9)	1.4	28.3 (20.0-40.0)	1.4	11.9 (7.8-18.2)	1.7	20.0 (12.3-32.6)	2.8
+ Sodium thiosulphate	1000	14.2 (6.4-31.5)	1.2	23.8 (16.8-35.2)	1.2	11.9 (7.8-18.2)	1.7	28.3 (16.3-49.3)	4.0

* All compounds were administered as 30 min pretreatment. Values are mg/kg. Figures in parentheses are fiducial limits.
SM = sulphur mustard, Protection Index (PI) = LD_{50} with treatment/LD_{50} without treatment

Table 3. Protective effect of various antidotes (intraperitoneal administration) against percutaneously administered HN-2 and sulphur mustard in mice.

Chemicals/ Drugs	Oral Dose*	LD_{50} of HN-2	PI	LD_{50} of SM	PI
Agent only	-	20.0 (12.7-32.6)	-	7.1 (5.0-10.0)	-
+ DRDE-07	125	16.8 (11.0-25.7)	0.8	63.5 (28.1-143.8)	8.9
+ DRDE-09	137	20.0 (12.7-32.6)	1.0	63.5 (28.1-143.8)	8.9
+ DRDE-10	131	16.8 (11.0-25.7)	0.8	89.8 (42.3-190.1)	12.6

Chemicals/ Drugs	Oral Dose*	LD_{50} of HN-2	PI	LD_{50} of SM	PI
+ DRDE-21	127	16.8 (11.0-25.7)	0.8	20.0 (12.0-31.5)	2.8
+ DRDE-30	110	20.0 (12.7-32.6)	1.0	56.6 (29.8-107.3)	8.0
+ DRDE-35	115	20.0 (12.7-32.6)	1.0 (32.2-70.4)	47.6	6.7
+ Amifostine	93	23.8 (15.6-36.6)	1.2 (12.0-31.5)	20.0	2.8
+ NAC	125	20.0 (12.7-32.6)	1.0 (12.7-31.5)	20.0	2.8
+ Melatonin	125	23.8 16.1-35.2	1.2	40.0 24.5-65.3	5.6
+ STS	500	23.8 (16.1-35.2)	1.2 (5.0-10.0)	7.1	1.0

* All compounds were administered as 30 min pretreatment. Values are mg/kg. Figures in parentheses are fiducial limits.

SM = sulphur mustard, Protection Index (P.I.) = LD_{50} with treatment/LD_{50} without treatment

sulphur mustard toxicity [18]. It was also found that other analogues of DRDE-07 are effective and give good protection, but better one is DRDE-07 against sulphur mustard toxicity. Since the action of nitrogen mustards and sulphur mustard is expected to be similar, amifostine, DRDE-07, and related compounds are a logical choice to test against nitrogen mustards toxicity.

DRDE-07 and its analogues have been found to be the most effective compounds for sulphur mustard systemic toxicity. However, none of the compounds was found as promising antidote for nitrogen mustard toxicity. But, these compounds showed slightly more protection than already recommended drugs like amifostine, N-acetyl cysteine, sodium thiosulphate, and melatonin against percutaneously administered nitrogen mustards. This indicates that nitrogen mustards toxicity pattern is somewhat different from sulphur mustard. However, DRDE-30 and DRDE-35 were over all better and gave marginal protection against HN-2 and HN-3. Probably these compounds may be beneficial in correcting the biochemical changes induced by sublethal doses of sulphur mustard as well as nitrogen mustards.[20] These two compounds also have better safety in terms of LD_{50} by oral and intraperitoneal routes.

ACKNOWLEDGMENT

The authors are thankful to Dr S.J.S. Flora, Head, Division of Pharmacology and Toxicology, Defence Research and Development Establishment, Gwalior for providing all necessary facilities to conduct this study.

REFERENCES

1. Smith, W.J.; Gross, C.L.; Chan, P. & Meier, H.L. The use of human epidermal keratinocytes in culture as a model for studying the biochemical mechanisms of sulphur mustard toxicity. *Cell. Biol. Toxicol.*, 1990, **6**, 285-91.
2. Wormser, U.; Brodsky, B.; Green, B.S.; Arad-Yellin, R. & Nyska, A. Protective effect of povidone-iodine ointment against skin lesions induced by sulphur and nitrogen mustards and by non-mustard vesicants. *Arch. Toxicol.*, 1997, **71**, 165–70.
3. Chabner, B.A.; Philip, C.A.; Druker, B.I.; Michaelson, M.D.; Mitsiades, C.S.; Goss, P.E.; Ryan, D.P.; Ramachandra, S.; Richardson, P.G.; Supko, J.G. & Wilson, W.H. Anti-neoplastic agents. *In* Goodman and Gilman's the pharmacological basis of therapeutics, edited by. Brunton, L.L.; Parker, K.L; Murri, N. & Blumenthal, D.K. Ed. 11. McGraw-Hill Medical Publishing Division, USA, 2006. pp. 1315 – 403.
4. Naujokaitis, S.A.; Fisher, J.M. & Rabinovitz, M. Protection of murine L1210 leukemia and bone marrow progenitor cells against mechlorethamine and inhibition of choline uptake as a structure-activity relationship of 2-dimethylaminoethanol and its analogues. *J. Pharm. Sci.*, 1984, **73**, 34-9.
5. Papirmeister, B.; Feister, A.F.; Robinson, S.I. & Ford, R.D. Medical defense against mustard gas: toxic mechanisms and pharmacological implications. CRC Press, Boca Raton, FL. 1991. pp. 174-99.
6. Casillas, R.P.; Kiser, R.C.; Truxall, J.A.; Singer, A.W.; Shumaker, S.M.; Niemuth, N.A.; Ricketts, K.M.; Mitcheltree, L.W.; Castrejon, L.R. & Blank, J.A. Therapeutic approaches to dermatotoxicity by sulfur mustard I. Modulaton of sulphur mustard-induced cutaneous injury in the mouse ear vesicant model. *J. Appl. Toxicol.*, 2000, **20**, S145-51.
7. Sawyer, T.W.; Hancock, J.R.; & D'Agostino, P.A. L-thiocitrulline: A potent protective agent against the toxicity of sulphur mustard in vitro. *Toxicol. Appl. Pharmacol.*, 1998, **151**, 340-46.
8. Sawyer, T.W. & Risk, D. Effects of selected arginine analogues on sulphur mustard toxicity in human and hairless guinea pig skin keratinocytes. *Toxicol. Appl.*

Pharmacol., 2000, **163**, 75-85.
9. Capizzi, R.L. Recent developments and emerging options: the role of amifostine as a broad-spectrum cytoprotective agent. *Semin. Oncol.*, 1999, **26**, 1-2.
10. Vijayaraghavan, R.; Kumar, P.; Joshi, U.; Raja, S.K.; Lakshmana Rao, P.V.; Malhotra, R.C. & Jaiswal, D.K. Prophylacvtic efficacy of amifostine and its analoges against sulphur mustard toxicity. *Toxicology,* 2001, **163**, 83-91.
11. Kumar, O.; Sugendran, K. & Vljayaraghavan, R. Protective effect of various antioxidants on the toxicily of sulphur mustard administered to mice by inhalation or percutaneous routes. *Chem. Biol. Interact.*, 2001, **134**, 1-12.
12. Vojvodic, V.; Milosavljevic, Z.; Boskovic, B. & Bojanic, N. The protective effect of different drugs in rats poisoned by sulfur and nitrogen mustards. *Fundam. Appl. Toxicol.*, 1985, **5**, S160-68.
13. Dorr, R.T.; Soble, M. & Alberts, D.S. Efficacy of sodium thiosulphate as a local antidote to mechlorethamine skin toxicity in the mouse. *Cancer Chem. Pharmacol.*, 1988, **22**, 299-302.
14. Khan, S.; Ramwani, J.J. & O'Brien, P.J. Hepatocyte toxicity of mechlorethamine and other alkylating anticancer drugs. Role of lipid peroxidation. *Biochem. Pharmacol.*, 1992, **43**, 1963-67.
15. Hotiboglu, I.; Michich, E.; Moore, G.E.; Nichol, C.A. Use of sodium thiosulphate as a neutralising agent during regional administration of nitrogen mustard: an experimental study. *Am. J. Surg.*, 1962, **156**, 994-1001.
16. Dacre, J.C. & Goldman, M. Toxicology and pharmacology of the chemical warfare agent sulphur mustard. *Pharmacol. Rev.*, 1996, **48**, 289-326.
17. Bhattacharya, R.; Lakshmana Rao, P.V.; Pant, S.C.; Kumar, P.; Tulswani, R.K.; Pathak, U.; Kulkarni, A. & Vijayaraghavan, R. Protective effects of amifostine and its analogues on sulphur mustard toxicity in vitro and in vivo. Toxicol. *Appl. Pharmacol.*, 2001, **176**, 24-33.
18. Kulkarni, A.S.; Vijayaraghavan, R.; Pathak, U.; Raza, S.K.; Pant, S.C.; Satish, H.T.; Malhotra, R.C. & Prakash, A.O. Evaluation of analogues of DRDE-07 as prophylactic agents against the lethality and toxicity of sulphur mustard administered through percutaneous routes. *J. Appl. Toxicol.*, 2006, **26**, 115-25.
19. Gad, S.C. & Weil, C.S. Statistics for toxicologists. *In* Principles and methods of toxicology, edited by Hayes, A.W., Ed. 2. Raven Press, New York, 1989. pp. 463-67.
20 Sharma, M.; Vijayaraghavan, R. & Gautam, A. DRDE 07 and its analogues as promising cytoprotectants to nitrogen mustard (HN-2)- an alkylating anti-cancer and chemical warfare agent, *Toxicol. Lett*, 2009, (*In Press*)
21. Pathak, U.; Raza, S.K.; Kumar, P.; Vijayaraghavan, R. & Jaiswal, D.K. Evaluation of amifostine and its analogues against sulphur mustard intoxication, *Def. Sci. J.*, 2002, **52**, 439-43.
22. Pathak, U.; Raza, S.K.; Kulkarni, A.S.; Vijayaraghavan, R.; Kumar, P. & Jiaswal, D.K. Novel S-substituted aminoalkylamino ethanethiols a potential antidotes against sulfur mustard toxicity. *J. Med. Chem.*, 2004, **47**, 3817-822.

Contributors

Dr Manoj Sharma received his MPharma (Pharmacology) from Rajiv Gandhi University of Health Sciences, Bangalore in 2003 and PhD from Jiwaji University in 2009. He joined Defence Research and Development Establishment (DRDE), Gwalior, as Junior Research Fellow, and presently, working as Asst. Professor in the Department of Pharmacology in Shri RNS institute of Pharmaceutical Sciences and Technology, Gwalior. His area of research include: biochemical changes induced by chemical warfare agents and screening of antidote.

Dr R Vijayaraghavan received his MSc (Pharmacology) from JIPMER, Pondicherry, and PhD from the Jiwaji University, Gwalior. He worked as a Research Associate at the University of Pittsburg, USA, during 1991–1993. Currently, he is Director of DRDE, Gwalior. His areas of research include: Safety evaluation of chemicals and development of antidotes against chemical warfare agents. He has more than 100 research papers published in various national/international journals.

Dr (Ms) Uma Pathak is scientist 'D' at DRDE, Gwalior. She did her MSc in Organic Chemistry from Kumaun University in 1992 and PhD from Jiwaji University in 2003. Her arears of research include: development of novel synthetic strategies in organosulfur transformations and drug development against toxicants such as Sulfur mustard and toxic metals. She has published several papers in highly reputed international and national journals and has many national and international patents to her credit.

Dr K. Ganesan received his MSc (Chemistry) from Bharathiar University, Coimbatore and PhD from Jiwaji University, Gwalior. He joined DRDO at Defence Research and Development Establishment (DRDE), Gwalior in 1989. Presently, he is Scientist E in Synthetic Chemistry division. He has more than 45 research papers in reputed journals and 25 national/multinational patents to his credit. He got *DRDO Technology Awards* (2004 & 2005) and *DRDO Science Day Oration Award (2008)*. His areas of work include: Defence against chemical warfare agents and development of new mosquito control techniques. Besides he is also engaged in NBC related activities at the National Disaster Management Authority.