MUTAGENICITY OF NN-DIALKYLAMINOALKYL CHLORIDES

C.J. Soper, E.V. Hoxey and R.T. Parfitt, School of Pharmacy and Pharmacology, University of Bath, BA2 7AY

The cyclic aziridinium ion is a powerful alkylating agent of functional nucleophilic groups. The capacity to form this ion and to alkylate DNA is a feature of a number of potent mutagens and carcinogens e.g. ethylenimine, triethylene melamine and the nitrogen mustards. NN-Dialkylaminoalkyl chlorides are widely used for the addition of sidechains to phenothiazines, thioxanthenes and tricyclic antidepressants, and in the synthesis of drugs such as pethidine and methadone. They are stable compounds and may well persist through the synthesis and occur as trace contaminants in the final product. It can also be predicted that a number of these compounds may form the aziridinium ion. This work investigates the correlation between mutagenicity and the ability to form the aziridinium ion in a series of NN-Dialkylaminoalkyl chlorides.

It was anticipated that the induced mutations would be of the base-change type and so the test strains chosen were E.coli WP2 and E.coli WP2 uvrA. The mutagenicity test used was the Gatehouse 'microtitre' modification of the Green fluctuation test. This test detects very small increases over the spontaneous mutation rate and is extremely sensitive. It involves chronic treatment of the test strains with low doses of mutagen and thus corresponds more closely to the environmental situation. The test compound in 20 ml. Davis-Mingioli salts supplemented with 0.2 $\mu g\ ml^{-1}$ L-tryptophan and 0.8% w/v glucose was inoculated with 5 x 10^5/ml. log phase test organisms. 96 x 0.2 ml. aliquots were distributed into the wells of a microtitre ^{R}plate. After incubation at 37^{o}C for 72 hrs. the number of wells showing growth in test and control plates was determined and the significance tested by χ^2. The results are summarised in Table I.

Table I. Mutagenicity of NN-Dialkylaminoalkyl chlorides in the fluctuation test.

	Compound	conc $Mol.L^{-1}$	Significance (probability) WP2	WP2 uvrA
I	$(CH_3)_2NH$	10^{-2}	n.s.	n.s.
II	$(CH_3)_2NCH_2CH_2Cl$	10^{-5}	0.1%	0.1%
		10^{-6}	n.s.	0.1%
III	$(C_2H_5)_2NCH_2CH_2Cl$	10^{-5}	0.1%	0.1%
		10^{-6}	n.s.	0.1%
IV	$(CH_3)_2NCH_2CH_2CH_2Cl$	10^{-2}	n.s.	n.s.
V	$(CH_3)_2NCH_2CH(CH_3)CH_2Cl$	10^{-2}	n.s.	n.s.
VI	$(CH_3)_2NCH_2CH(CH_3)Cl$	10^{-5}	0.1%	0.1%
		10^{-6}	n.s.	0.1%

I, IV and V are negative in the test at concentrations up to 10^{-2} $Mol.L^{-1}$. They are also unable to form an aziridinium ion. II, III and VI are able to form the ion and are predictably positive mutagens at concentrations as low as 10^{-6} $Mol.L^{-1}$ Substitution of ethyl groups for methyl groups in II and III has no effect on the mutagenicity of the NN-Dialkylamino ethyl derivative. The increased sensitivity of E.coli WP2 uvrA to II, III and VI suggests that the base-pair mutations induced by these chemicals are subject to excision repair.

Gatehouse, D. (1978) Mutat Res., 53, 289-296

Green, M.H.L., Muriel, W.J. and Bridges, B.A. (1976) Mutat. Res., 38, 33-42