Formaldehyde as a Possible Carcinogen

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INTRODUCTION

Formaldehyde is used widely as a germicide, fungicide, insecticide and preservative, in addition it is an important intermediate in many industrial processes (1-3). It is to be expected, therefore, that exposure to this chemical is very common.[1] Human exposure to low levels of this substance appears to be safe except for occasional hypersensitivity reactions. It has been known, however, for a number of years (4, 5) that formaldehyde was a mutagen[2], yet despite the known detrimental effects of many mutagens on human health, no effort has been made to reevaluate and possibly regulate the wide-spread usage of formaldehyde.

Recent studies in this Laboratory have been concerned with the detection of potential carcinogens using a microbial assay system (8). The procedure used is based upon the assumption that the activity of chemical oncogens derives from their ability to alter the DNA of living cells. Normal cells are able, to some extent, to counter the detrimental effects of such agents by repairing the damaged portions of their DNA. However, cells deficient in their ability to repair efficiently damage to their DNA will display an increased sensitivity towards agents which react with their DNA. DNA polymerase is one of the enzymes involved in DNA repair (9, 10) and it has been shown that cells lacking this enzyme (pol A^- cells) are much more sensitive than their pol A^+ parents to a number of agents (radiations, radiomimetic agents and carcinogens (8, 10-12)) known to react with the cellular DNA. On the other hand the two strains exhibited equal sensitivities towards (non-oncogenic) substances known to interfere with structures other than the cellular DNA (8). These observations form the basis of our screening procedure (8). When this technique was applied to the detection of potential carcinogens in the environment, a number of substances heretofore considered as "safe" (i.e. non-oncogenic) were incriminated. One of these, first detected by this

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[1] Hexamethylenetetramine and paraformaldehyde also release formaldehyde under appropriate conditions, thereby further increasing the possibility of exposure to this agent.

[2] The basis of this mutagenic action appears to be a reaction between formaldehyde and the amino groups of the DNA bases (6, 7).

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method, was tested in animals in which it was shown to be a tumorigen (M.D. Anderson and H.S. Rosenkranz, unpublished results). This then established the validity of the procedure.

Experimental

E. coli W3110 thy$^-$ (pol A$^+$) and its DNA polymerase deficient derivative, E. coli p3478 (pol A$_1^-$) were obtained from Dr. John Cairns, Cold Spring Harbor Laboratory (10). Portions (0.1 ml) of bacterial cultures grown in medium HA (13) supplemented with thymine (5μg/ml) were spread onto the surface of agar plates of the same composition (14). When the surface of the agar had dried, a sterile disc impregnated with the substance to be tested was placed on the agar and the plates were incubated at 37°C for 7 hours at which time the diameter of the zones of inhibition was measured.

Results and Discussion

The data of Table 1 indicate that formaldehyde preferentially inhibited the growth of the pol A$^-$ strain. Although the difference in the size of the zones of inhibition is small, it is reproducible. This small difference presumably reflects the fact that formaldehyde reacts with cellular structures other than DNA as well (e.g. proteins). The preferential inhibition of the pol A$^-$ strain by formaldehyde is a property also exhibited by the well-known carcinogens methyl methanesulfonate and N-hydroxylaminofluorene. On the other hand in confirmation of earlier results, it was shown (Table 1) that the two strains exhibited equal sensitivities to agents known not to affect cellular DNA (streptomycin, ampicillin and cycloserine).

TABLE 1

Effect of Formaldehyde on the Growth of DNA Polymerase-Deficient Cells

Agent	Diameter of Zone of Inhibition (mm)	
	Parent	Mutant Strain
Formaldehyde	59	62
Methyl methanesulfonate	42	56
N-Hydroxylaminofluorene	0	12
Streptomycin	26	26
Ampicillin	28	28
Cycloserine	62	62

In view of the present findings and because the procedure used seems to be quite reliable for detecting carcinogens, it would seem that the continued universal use of formaldehyde requires reevaluation and monitoring as exposure to even low levels of this substance might be deleterious especially if it occurs over prolonged periods of time, a situation which probably increases the chance of carcinogenesis.

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