The obtained results reveal dose dependence for both lethality and teratogenic outcome. Types of teratomas indicate that most of them are chondropathic and affect skeleton causing different malformations, evisceration and runting in somatic development. Further experimentation with some compounds derived from erythromycin point to the fact that carbamide induces skeletal malformations and isoniazide leads to evisceration.

Mutation Research 38, p112, 1976

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Chromosome studies in workers exposed to vinyl-chloride

Chromosome analysis have been done on 48-h lymphocyte cultures from 39 workers in the PVC factory in Norway, and on 16 control persons matched to sex and age. Bone marrow samples were studied in four cases.

Measurements of exposure are unfortunately not available before 1974.

Hundred cells per individual were scored for breaks, gaps rings, dicentrics, fragments, chromatide exchanges, and "stable" rearrangements. Breaks and gaps were the predominant aberrations in the cells both in the controls and in the workers. "Stable" rearrangements were found in more cells than was expected. Gaps are not included in the results.

The results are presented as number of cells with aberrations, and also considered as total breaking events per 100 cells. The number of cells with aberrations and total breaking events are not greatly increased for the workers compared with the controls. The results were tested statistically by a Wilcoxon two-sample test, which showed that workers scored significantly higher on a 2.5% level. The results are discussed.

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Cytogenetic investigations on leucocytes of workers from a cadmium plant

Chromosome analysis has been performed on workers of a cadmium plant, who were exposed to fumes and dust of cadmium and lead. The 35 workers were classified, according to the type and duration of exposure, into a group (cadmium service) of 23 people exposed to high levels of lead and cadmium in the absence of zinc and into a group of 12 rolling-mill workers subjected mostly to zinc but also to lower levels of lead and cadmium. A higher yield of severe chromosome anomalies (chromatid exchange, disturbance of spiralisation, chromosome translocation, ring and dicentric chromosomes) together with a total lower number of structural aberrations was observed in the cadmium workers when compared to the rolling-mill group.

These data will be discussed together with the results obtained in a previ-

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A.G. Searle and C.V. Beechey, MRC Radiobiology Unit, Harwell (U.K.)

Cytogenetic effects of Plutonium-239

Although plutonium is known to be highly carcinogenic, its mutagenic properties have been little studied. However, recent work at this Unit by Green et al., (Nature, 255,77) has shown that in the mouse testicle plutonium tends to concentrate in the interstitial tissue, thus increasing the α-particle dose to the genetically significant spermatogonial stem-cells above the expected level. We have therefore started to gather information on the rate of induction of chromosome aberrations in the germ-cells of male mice which have been exposed for long periods to plutonium-239, given by intravenous injection. Our results so far suggest that α-particles behave like fission neutrons in being highly effective for translocation induction.

They are also consistent with the operation of a dose inhomogeneity factor of the magnitude suggested by Green and co-workers. Evidence for the induction of chromosome fragments and sperm-head abnormalities was also obtained.

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24 Mutation Research 38, 113, 1976

U. Rannug and C. Ramel, Environmental Toxicology, Unit, Wallenberg Laboratory, Stockholm (Sweden)

The mutagenicity of waste products from the vinyl chloride industries

Vinyl chloride, which is synthesized and used in large quantities, has previously been shown to possess carcinogenic and mutagenic properties. In industrial processes involving vinyl chloride, there is a risk that also by-products with carcinogenic and mutagenic properties are formed.

The manufacturing of vinyl chloride from acetylene, ethylene or from a mixture of these substances gives rise to a waste product, the so called EDC-tar, containing ethylene dichloride as one of its main components. This waste product has been dumped in large quantities in the sea (Jensen et al., 1975).

EDC-tar was tested for mutagenicity with one of the strains (TA1535) in the Salmonella test system (Ames et al., 1973) This strain responds to base-pair substitutions in DNA. Ethanol, dimethyl sulfoxide (DMSO) and Tween 80 were used to dissolve or emulse the tar. The treatment gave mutagenic effect which was approximately of the same magnitude during these three conditions.

When, however, a microsomal fraction from rat liver plus a NADPH-generating system was added, the EDC-tar exhibited a considerably stronger mutagenic effect. The results suggest that there are direct as well as indirect mutagenic components in the EDC-tar.

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Covalent binding of haloalkanes to liver constituents, but absence of mutagenicity on bacteria in a metabolizing test system

After intraperitonel injection of labelled CCl_4, $CHCl_3$, $CFCl_3$, and halothane to mice, ^{14}C is preferentially bound to liver endoplasmic protein and lipid. A considerable activity is also associated with mitochondrial constituents.

The covalent binding of ^{14}C from the labelled haloalkanes in suspensions of isolated rabbit liver microsomes and NADPH after 30-min incubation was in nmol per mg of protein (lipid): CCl_4: 15 (58); $CHCl_3$: 3.4 (3.2); trichlorofluoromethane 6.5 (30); halothane 2.3 (10). The results prompted us to investigate the potential mutagenic activity of these haloalkanes with bacterial tester strains added to the microsomal incubates. *S. typhimurium* TA 1535 and *E. coli* K-12 were used to detect base pair substitution mutations, and *S. typhumurium* TA 1538 for the detection of frame shift mutations. Although metabolic activation of the test compounds dimethylnitrosamine and 3,4-benzopyrene induced base pair substitution and frame shift mutations respectively, no mutagenic activity of the haloalkane metabolities could be observed.

The primary reactive metabolic intermediates of the haloalkanes tested are assumed to be short living radicals and/or anions and carbenoid species which would not easily reach targets distant from the endoplasmic reticulum. In accordance, no significant binding of radioactivity was detected in added, soluble albumin or RNA in microsomal incubates with the labelled haloalkanes. On the other side, appreciable binding to mitochondrial protein and lipid points to possible stabilization and transport mechanisms of reactive haloalkane metabolites.

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Mutagenicity of industrial compounds: vinyl chloride, styrene and their possible metabolites

It has been proposed that mutagenicity tests are at present the most appropriate for the prescreening of substances for possible carcinogenic activity. It is therefore interesting to develop biological analyses to asses the mutagenic activity of toxic industrial compounds already known as human carcinogens or those compounds under suspicion.

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In our analyses we have applied mutagenicity methodologies in the study of vinyl chloride (human carcinogen) and to styrene (under carcinogenic analysis at present): the same analyses have been applied also to their possible metabolites (2-chloroethylene oxide, 2-chloroethanol, 2-chloroacetaldehyde, and styrene oxide) in order to correlate the mammalian metabolic fate of the compounds with their biological activity.

The compounds have been studied by means of liver microsomal assay and host mediated assay (mice) on employing as a test organism the yeast *S. pombe* and *S. cerevisiae* on which the induction of gene-mutations and of gene-conversions has been analyzed. Preliminary experiments have been done also with somatic mammalian cells (V79 chinese hamster), on which the induction of 8-azaguanine resistant clones has been assessed.

From our analyses it has been found that vinyl chloride is mutagenic in the presence of liver microsomal preparations (in vitro) or in the host mediated assay (in vivo); moreover the possible in vivo metabolite, 2-chloroethylene oxide, is reponsible for mutagenic activity. The styrene has been found inactive on yeast (± microsomes) or slightly active on hamster cells; styrene oxide, on the contrary, was found active in different biological systems. A comparison with known chemical mutagens will be reported.

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27 Mutation Research 38, 1976

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Mutagenic effects of vinyl chloride in *Drosophila melanogaster*

After the report 1974 of the carcinogenic effects of vinyl chloride in humans and in experimental rodents, genetic investigations on Salmonella of this laboratory (Rannug et al., 1974) as well as I.A.R.C. laboratory in Lyon (Bartsch et al., 1975) have shown that VC is converted to a mutagenic metabolite in liver microsomes.

In order to study the effect of VC in the gonads and the transmission of mutations to the next generation, tests with sex linked recessive lethals in Drosophila were performed by means of the Muller 5 method. Males were treated with doses of VC in the air for three hours and mated to Muller 5 females. A significant increase of recessive lethals was obtained both in the first and second generation after the treatment, indicating the induction of recessive lethal mosaics. The results are in accordance with the findings by Vogel (1974) that Drosophila exhibits a metabolic conversion of indirect carcinogens, resembling the metabolic activation in mammals.

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