ABSTRACT

A 48-h treatment with vinyl acetate (0.05–1 mM) induced a drastic increase in sister chromatid exchanges (SCEs) and (in first division cells) structural chromosome aberrations in cultured human lymphocytes. The effects were more pronounced in cultures of isolated lymphocytes than in whole-blood cultures. A distinct dose-dependent induction of SCEs similarly occurred in Chinese hamster ovary cells after a 24-h vinyl acetate treatment (0.125–1 mM). A pulse treatment of Chinese hamster ovary cells for 4 h also yielded a clear increase in SCEs, but at higher concentrations (0.3–5 mM). The presence of rat liver S9 mix enhanced the SCE-inducing effect of vinyl acetate in Chinese hamster ovary cells. Gas chromatographic analysis of human whole-blood lymphocyte cultures treated for 10–20 min with vinyl acetate (5.4 mM) revealed a rapid degradation of vinyl acetate and formation of acetaldehyde. During the 20-min observation period, no degradation of vinyl acetate or formation of acetaldehyde were observed in complete culture medium without blood, which suggested that the reaction was enzymatic. Acetaldehyde induced SCEs in human whole-blood lymphocyte cultures at concentrations (0.125–2 mM) comparable to those used for vinyl acetate. The results indicate that vinyl acetate induces chromosome damage in cell cultures through enzyme-mediated hydrolysis to acetaldehyde.

INTRODUCTION

The epoxidation of the vinyl moiety appears to be the most important metabolic activation reaction involving vinyl compounds (1). For example, two important plastic monomers, vinyl chloride and styrene (vinyl benzene), both mutagenic in a number of test systems, are converted by microsomal monooxygenases to corresponding epoxides (1–3). The oxidation of the vinyl double bond may in some cases occur through nonmicrosomal routes. Styrene is metabolized to styrene-7,8-oxide in human blood by the action of erythrocytes in a reaction probably catalyzed by oxyhemoglobin (4). Consequently the induction of SCEs by styrene in human whole-blood lymphocyte cultures depends on the number of erythrocytes present (5, 6).

Vinyl acetate (acetic acid vinyl ester), used, e.g., for the manufacture of polyvinyl acetate and polyvinyl alcohol, is another important vinyl monomer. In spite of the industrial importance of vinyl acetate, only a limited amount of information is available as to the genotoxic effects of this compound. It was not mutagenic to Salmonella typhimurium (1, 7–9), but workers exposed to vinyl acetate were reported to have an increase in chromosome aberrations in their blood lymphocytes (10). Inhalation of vinyl acetate did not produce cancer in rats (11), while rats receiving vinyl acetate in their drinking water were reported to develop tumors in the uterus, thyroid, and liver (12).

In principle vinyl acetate could be epoxidized at the vinyl group, through microsomal or nonmicrosomal routes. However, in the case of vinyl acetate, epoxidation seems to be of only theoretical importance. As early as 1959 Filov suggested that vinyl acetate is rapidly hydrolyzed enzymatically to acetic acid and, via unstable vinyl alcohol to acetaldehyde (13, 14). He detected acetaldehyde in samples of human and rat plasma and whole blood 3 min after the addition of vinyl acetate, but not in heat-inactivated plasma. Acetaldehyde is a well-known mutagen (15, 16) and is thus a probable reactive metabolite of vinyl acetate.

In the present paper we have studied the cytogenetic effects of vinyl acetate in cultures of human lymphocytes and CHO cells. If microsomal epoxidation actually were important for the metabolic activation of vinyl acetate, a positive result in the cytogenetic tests would probably be expected only after the use of a metabolic activation system. If erythrocytes had the capacity to activate vinyl acetate, more chromosome damage would be observed in lymphocytes cultivated with whole blood than in isolated lymphocytes. On the other hand, if the hydrolysis of the ester bond were the critical reaction, an increase in chromosome aberrations and SCEs could probably be expected without exogenous metabolic activation. In addition to cytogenetic analysis, we utilized gas chromatography to measure the possible degradation of vinyl acetate and formation of acetaldehyde in human whole-blood lymphocytes cultures.

MATERIALS AND METHODS

Test Chemicals. Vinyl acetate (>99% pure), containing 0.0015% of hydroquinone as a stabilizer, was obtained from Fluka (Buchs, Switzerland). For treatment of the cultures, vinyl acetate was dissolved in acetone; several solutions, from 0.5 to 0.05 ml/ml, were used. Acetaldehyde (99.5%) was a product of Merck (Darmstadt, West Germany); two solutions, 0.1 and 0.01 ml/ml prepared in acetone, were used for the treatments. All solutions were made shortly before use. Because of the high volatility of acetaldehyde (boiling point, 20–21°C), its solutions were prepared and kept in an ice bath. Cyclophosphamide was obtained from Läätke/Farmsos-Yhtymä Oy (Turku, Finland) and was dissolved (10 mg/ml) in equal volumes of 0.9% (w/v) NaCl solution and McCoy's Medium 5A (Grand Island Biological Co., Glasgow, United Kingdom).

Studies with Human Lymphocytes. Lymphocytes were cultured in the dark at 37°C in air-tight glass injection bottles (20 ml) containing 6 ml of growth medium consisting of (in 100 ml) 15 ml of heat-inactivated fetal calf serum (Grand Island Biological Co.), 1 ml of phytohemagglutinin (Wellcome, Beckenham, Kent, United Kingdom), 2 ml of 5-bromodeoxy-
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uridine (Calbiochem, La Jolla, CA; 0.25 mg/ml in sterile water: final concentration, 5 μg/ml), and 82 ml of RPMI Medium 1640 (with L-glutamine; Grand Island Biological Co.). For whole-blood cultures, 0.27 ml of heparinized blood from a healthy male donor (age 30) was used. The final volume of these cultures was thus 6.27 ml. The number of leukocytes and erythrocytes in the blood samples was evaluated by the Coulter ZM Counter (Luton, United Kingdom).

Purified lymphocyte cultures were established from lymphocytes isolated with Ficoll-Paque (Pharmacia Fine Chemicals, Uppsala, Sweden) as described elsewhere (5). The numbers of leukocytes in the suspension of isolated cells were counted by the Coulter Counter and the proportions (9.1-19.3%) of isolated cells were lymphocytes, 4% erythrocytes, and 1% monocytes. The number of leukocytes in the purified cultures was adjusted according to their number in whole-blood cultures. The volume of the isolated lymphocyte cultures was 6.5 ml. On the average the cultures contained, per ml, 200,000 leukocytes and 200 million (whole blood), or below 8,000 (isolated cultures) erythrocytes.

The cells were treated 24 h after starting the cultures. The final concentrations of the test chemicals in the cultures were 0.05, 0.1, 0.2, 0.5, and 1 mM for vinyl acetate, and 0.063, 0.125, 0.25, 0.5, and 2 mM for acetaldehyde (whole-blood cultures only). Duplicate cultures were used for each treatment. Control cultures were treated with acetone (9.1–19.3 mM). The incubation was continued for an additional 48 h, making a total of 72 h. Cell harvest, slide preparation, and staining were performed as described earlier (17).

Studies with CHO Cells. The cultures were set up as described by Hytönen et al. (18) and treated 24 h after initiation. In the first experiment the duration of the treatment was 24 h. The vinyl acetate concentrations used were 0.125, 0.25, 0.5, 1, and 2 mM. In the second experiment, the cells were first treated in serumless medium, caps of the flasks tightly closed, with different concentrations of vinyl acetate (0.31, 0.63, 1.25, 2.5, and 5 mM) for 4 h, after which they were rinsed and allowed to recover in complete medium for 24 h. The latter experiment was performed with and without 59 mix derived from the livers of Wistar rats induced with Aroclor 1254 (Analyabs, Inc., North Haven, CT) as shown elsewhere (18, 19). 59 mix was prepared using a method slightly modified from that of Nachtmann and Wolff (20). The modifications were the use of MgSO4 (Merck) instead of MgCl, and the addition of 55 μl of McCoy's Medium 5A/ml (Grand Island Biological Co.). Duplicate cultures were used for all treatments. Control cultures were treated with acetone (27 mM). In the 4-h experiment, cyclophosphamide (10 mM) was used as a positive control agent. Cell harvest, slide preparation, and staining were performed as described previously (17, 18).

Chromosome Analysis. All microscopic analyses were performed on coded slides. One microscopist scored SCEs in human lymphocytes, another scored scored chromosome aberrations, and a third scored SCEs in CHO cells.

For the analysis of SCEs, 25–50 harlequin-stained cells (30 for CHO cells) were scored, whenever possible, from each of the duplicate cultures. Cell cycle delay was simultaneously evaluated by counting the number of first, second, and third (or further) division cells from 100 metaphases/culture. These data were transformed into cell proliferation indexes ("replication indexes") as described by Böhlke et al. (16). This index represents the average number of replications completed by the cells during 5-bromodeoxyuridine supplementation.

For the analysis of structural chromosome aberrations in first division cells of the human whole-blood lymphocyte cultures treated with vinyl acetate, 100 cells/culture, as a rule, was inspected for the presence of different categories of chromosome- and chromatid-type aberrations according to criteria suggested by Evans and O'Riordan (21). For each treatment a total of 200 cells was analyzed. The statistical analysis of the SCE data was performed according to 1-tailed t test (22). The frequencies of cells with chromosome aberrations were compared using Fisher's exact probability test (22).

Gas Chromatographic Measurements. The gas chromatographic measurements were performed according to a head-space method based on the procedure of Mendenhall et al. (23). The concentrations of vinyl acetate and acetaldehyde were determined, after the addition of vinyl acetate (1 μl; final concentration, 5.4 mM), from 2-ml aliquots (in air-tight 20-ml glass injection bottles) of RPMI Medium 1640 (Grand Island Biological Co.) containing 0.15 ml of heat-inactivated fetal calf serum/ml (Grand Island Biological Co.), with or without 0.1 ml of heparinized whole blood from a 35-year-old female donor. The reaction was stopped either immediately (after 10 s), or after various periods of incubation at 37°C (2, 5, 10, 15, and 20 min) by adding 1 ml of a mixture (1:3, v/v) of 40 mM thioicurea (Union Chimique, Brussel, Belgium) and 0.6 M perchloric acid (Merck), and transferring the bottle to dry ice for 30 min. The sample was then incubated at 80°C for 30 or 60 min, after which a volume of 500 μl was collected by an air-tight syringe from the gas phase of the bottle for immediate gas chromatographic analysis of vinyl acetate and acetaldehyde. The determination was performed with a Hewlett-Packard Model 5740 A (Hewlett-Packard Co., Avondale, PA) gas chromatograph equipped with a flame ionization detector and a Carbowax 20 M column (2 m, 10%, on Chromosorb W, acid washed, silanized). The carrier gas was helium, column temperature was 80°C, injection temperature was 150°C, and detector temperature was 200°C. The concentrations of vinyl acetate and acetaldehyde were derived from the analysis of samples with known amounts of vinyl acetate and acetaldehyde in serumless RPMI Medium 1640. Retention time was 1.2 min for acetaldehyde and 2.8 min for vinyl acetate.

RESULTS

SCE Induction in Human Lymphocytes. In human whole-blood lymphocyte cultures (with 200 million RBC/ml), there was a very clear dose-dependent increase in SCEs after a 48-h treatment with vinyl acetate (Chart 1). The effect was statistically significant (P < 0.001) at 0.1 mM and higher concentrations. At 1 mM the number of SCEs/cell was almost 15 times the control frequency. According to the proliferation index, a toxic effect of vinyl acetate on cell division was apparent from concentrations of 0.5 mM and up. At 1 mM only 13 cells could be analyzed for SCEs.

In purified lymphocyte cultures (with 8000 RBC/ml), the dose-dependent effect of vinyl acetate on SCEs was still more pronounced than in whole-blood cultures (Chart 1). A 2.4-fold increase in SCEs was already present at the lowest concentration tested (0.05 mM); and at 0.5 mM the mean number of SCEs per cell was 10 times higher than in controls. The proliferation index decreased from concentrations of 0.2 mM and higher. In the controls, the frequency of SCEs was slightly, but nonetheless significantly (P < 0.01), higher in isolated lymphocytes than in lymphocytes cultivated with whole blood.

As with vinyl acetate, acetaldehyde also had a distinct dose-dependent effect on SCEs in human whole-blood lymphocyte cultures (Chart 2). The increase in SCEs was statistically significant (P < 0.001), beginning with a concentration of 0.125 mM. Concentrations from 0.5 mM and up clearly lowered the proliferation index.

Induction of Chromosome Aberrations in Human Lymphocytes. Vinyl acetate induced a very clear dose-dependent increase in chromosome aberrations in the first division lymphocytes of human whole-blood cultures treated for 48 h (Chart 3). A statistically significant effect (P < 0.001) on the number of aberrant cells (gaps included or excluded), and the number of cells carrying chromatid-type aberrations or chromatid-type exchanges, was observed at 0.5 mM. By far the most frequent type
of aberration was the chromatid-type break. At 1 mM, 84% of the cells were aberrant (gaps included, 2% in controls), 38% containing a chromatid-type exchange (none in controls). At this dose, chromosome-type breaks were also significantly increased (P < 0.001) (8% of cells, none in controls).

In cultures of isolated lymphocytes, vinyl acetate significantly (P < 0.001) increased the total number of aberrant cells (gaps included or excluded), and the number of cells containing chromatid breaks or chromatid exchanges (P < 0.05) beginning with 0.2 mM (Chart 3). Thus, vinyl acetate was clastogenic in isolated cultures at lower concentrations than in whole-blood cultures. From 0.5 mM and higher chromosome-type breaks were also increased (P < 0.001). At 1 mM, 97% of the cells included an aberration (gaps included, 5.5% in controls); 38% had a chromatid-type exchange. The frequencies of aberrant cells appeared to be higher in the controls of isolated cultures than in those of whole-blood cultures, but the differences were not statistically significant.

**SCE Induction in CHO Cells.** The effect of vinyl acetate on SCEs in CHO cells after a 24-h treatment was similar to the effect obtained with the 48-h treatment in human whole-blood cultures (Chart 4). The increase in SCEs was already significant (P < 0.001) at the lowest concentration tested (0.125 mM), and at 1 mM it was 11.6 times the control frequency. The proliferation index did not decrease below 1 mM.

The 4-h pulse treatment of CHO cells also led to a clear dose-dependent increase in SCEs, with or without S9 mix, but at higher concentrations than in the 24-h experiment (Chart 4). Both with and without S9 mix, a statistically significant (P < 0.001) response was present starting from the lowest concentration tested (0.3 mM). The use of S9 mix clearly enhanced the effect of vinyl acetate. According to the proliferation index, vinyl acetate began to have an inhibiting effect on cell proliferation at 1.25 mM with S9 mix and at 5 mM without it.

**Degradation of Vinyl Acetate and Formation of Acetaldehyde.** Within our observation period of 20 min, cultures containing blood showed a rapid disappearance of vinyl acetate and formation of acetaldehyde (Chart 5). In solutions containing culture medium and heat-inactivated serum but no cells, there was no degradation of vinyl acetate during this 20-min period.

**DISCUSSION**

The results of this study show that vinyl acetate is a very efficient inducer of both chromosome damage and SCEs in cultured mammalian cells. This effect is probably mediated by the rapid hydrolysis of vinyl acetate.

In the experiments with human lymphocytes, vinyl acetate produced chromosome damage without exogenous metabolizing systems, which indicates that the compound, not expected to be a direct mutagen, is activated in the *in vitro* system. The early studies of Filov (13) suggested that erythrocytes, as well as plasma proteins, contribute to the hydrolysis of vinyl acetate. In our study, vinyl acetate induced more SCEs and chromosome aberrations in isolated cultures than in whole blood. Conse-
Vinyl Acetate-Induced Chromosome Damage

Chart 3. Induction of chromosome aberrations in first division cells of human whole-blood lymphocyte cultures (---) and cultures of isolated lymphocytes (-----) after a 48-h treatment with vinyl acetate. Points, mean of 100-200 cells; bars, SE. •, aberrant cells including gaps; ▲, aberrant cells excluding gaps; ●, cells with chromatid-type exchanges.

Consequently, erythrocytes do not seem to play any important role in the activation of vinyl acetate. Because of their high number in a typical human whole-blood culture, erythrocytes may actually represent an important "inactivating" factor, offering additional targets for reactive molecules. Thus the lower SCE response in cultures of whole blood, as compared to those of purified lymphocytes, may represent a compromise between the hydrolysis ("activation") of vinyl acetate by plasma proteins, leukocytes, and erythrocytes and, on the other hand, trapping ("inactivation") of the reactive metabolite by erythrocytes.

The results of our experiments with CHO cells confirmed the findings of the lymphocyte assays. The high SCE induction, which occurred with or without metabolic activation, again suggested that vinyl acetate is activated by the cultured cells. In the 4-h pulse treatment, however, a clearly greater effect was received in the presence of S9 mix than in its absence. S9 mix obviously contains factors (probably esterases) capable of hydrolyzing vinyl acetate. The longer 24-h treatment yielded an increase in SCEs at lower concentrations than did the 4-h pulse treatment, which showed that the SCE-inducing effect of vinyl acetate depended on exposure time.

In our experiments with whole-blood lymphocyte cultures, we found that practically all of the vinyl acetate administered had been transformed into acetaldehyde within 15 min. This process appeared to be enzyme dependent, as no hydrolysis occurred in complete culture medium without blood. The rapid appearance of acetaldehyde in samples of blood, plasma, or erythrocytes treated with vinyl acetate was first shown by Filov in 1959 (13). He also reported that no formation of acetaldehyde could be detected in water, physiological saline, or heat-inactivated plasma within 3 min after vinyl acetate treatment, which pointed to an enzymatic reaction and to the unimportance of spontaneous hydrolysis during the short observation period. During longer intervals, spontaneous hydrolysis of vinyl acetate may, on the other hand, occur. Lijinsky and Reuber (12) reported that in water solution and at room temperature vinyl acetate decom-
It is supposed that vinyl acetate is attacked by a number of esterases. It was hydrolyzed by porcine pancreatic lipase (24) and was the best substrate, of a series of esters, for an acetyl-esterase purified from Sclerotinia fungus (25).

It is very likely that the chromosome damaging effects of vinyl acetate are due to acetaldehyde. At concentrations comparable to those used for vinyl acetate, acetaldehyde produced a clear increase in SCEs in human whole-blood lymphocyte cultures. Vinyl acetate was a somewhat more efficient inducer of SCEs than was acetaldehyde. This observation is probably explained by the high volatility and direct reactivity of acetaldehyde. Acetaldehyde has its boiling point at room temperature and is thus much more critical to handle than is vinyl acetate, which boils at 72°C. Consequently, the actual concentrations of the chemical may have been lower than expected in cultures treated with acetaldehyde. In vinyl acetate treatment, at least part of the acetaldehyde generated will be formed inside the target cells, which means fewer possibilities for binding to erythrocytes or growth medium components, and less distance to DNA than if the chemical is added to the culture in a reactive form. Lambert et al.5 showed, using the alkaline elution technique, that acetaldehyde and vinyl acetate induce SCEs at equimolar concentrations in cultures of isolated lymphocytes, which suggests that acetaldehyde binding to erythrocytes may be important.

Several earlier studies have shown that acetaldehyde is an effective inducer of chromosome aberrations, sister chromatid exchanges, and micronuclei in cultured cells such as lymphocytes, CHO cells, and rat skin fibroblasts (15, 16, 26–32). Acetaldehyde is also carcinogenic. Inhalation of acetaldehyde was reported to induce laryngeal tumors in Syrian golden hamsters and nose tumors in rats (33, 34).

All of the reactions of acetaldehyde with DNA have not yet been determined. Acetaldehyde was found to make reversible bonds, possibly Schiff bases, with exocyclic amino groups in the DNA bases adenine, cytosine, and guanine (35). After reduction with sodium borohydride, three stable products could be isolated. The main adduct was identified as N²-ethylguanosine, and the two minor ones were identified as N³-(3-hydroxybutyl)-guanosines formed by aldol condensation of two acetaldehyde molecules. Ristow and Obe (29) reported that acetaldehyde is able to induce cross-links between the complementary strands of DNA isolated from calf thymus or Bacillus brevis. Recently, Lambert et al.6 showed, using the alkaline elution technique, that acetaldehyde and vinyl acetate induce DNA cross-links in isolated human lymphocytes at equimolar doses. However, no direct strand breaking effect could be demonstrated for either of the compounds, which is in agreement with an earlier study which obtained a negative result for acetaldehyde in the alkaline elution assay with rat hepatocytes (36). It is probable that the clear clastogenic effects of acetaldehyde, and thus also of vinyl acetate, result from the cross-linking ability of acetaldehyde; cross-linking agents are usually very effective inducers of SCEs and chromosome aberrations.

In spite of the well-documented mutagenicity of acetaldehyde, only one positive short-term assay, on enhancement of viral transformation in Syrian golden hamster cells (37), has been published on vinyl acetate. In four independent studies with the Salmonella-microsome test, vinyl acetate gave no indication of mutagenicity with or without S9 mix (1, 7–9). These negative results would appear to conflict with the clear clastogenicity of vinyl acetate found in the present paper. Our results suggest that S9 mix is able to activate vinyl acetate; thus it is probable that acetaldehyde is also formed in bacterial assays in the presence of S9 mix. Acetaldehyde is itself, however, at best only a weak mutagen in the standard Salmonella plate test (38). The low mutagenicity of acetaldehyde may be related to the poor sensitivity of the conventional Salmonella strains to cross-linking agents, to the possible low capacity of acetaldehyde to induce gene mutations, or, especially, to the high volatility of acetaldehyde. When the treatment was carried out in stopped test tubes, acetaldehyde clearly increased mutations in Escherichia coli (15).

Our unpublished results6 suggest that vinyl acetate induces the formation of micronuclei in the polychromatic erythrocytes of C57BL/6 mice after a single i.p. injection. This effect is most probably mediated by acetaldehyde. Filov (13) suggested that vinyl acetate is converted into acetaldehyde very rapidly in vivo in rats, possibly through the action of unspecific esterases in blood (14). Acetaldehyde has been found to induce SCEs in the bone marrow of mice and Chinese hamsters after i.p. exposure (39, 40). The formation of acetaldehyde is also likely to take place in humans exposed to vinyl acetate. If this reaction occurred mainly in blood, the acetaldehyde formed would be expected to have an effect on leukocyte chromosomes. In fact, it has been reported that workers exposed to vinyl acetate have increased chromosome aberrations in peripheral lymphocytes (10).

Acetaldehyde is the key metabolite of both vinyl acetate and ethanol. This would suggest that ethanol is also a powerful clastogen. In vivo ethanol is clearly a less effective inducer of chromosome damage than is acetaldehyde or vinyl acetate. It does, however, increase SCEs and chromosome aberrations in cultured human lymphocytes without exogenous activation, and SCEs in CHO cells in the presence of S9 mix (26, 28, 30, 41, 42). The difference in effectiveness between ethanol and its reactive metabolite is possibly due to the poor transformation of ethanol to acetaldehyde in cell cultures. For example in mitogen-stimulated mouse spleen cells, ethanol was not metabolized during a 72-h observation period (43); and in cultures of CHO cells, acetaldehyde production from ethanol by rat liver S9 mix was much slower than we observed for vinyl acetate in cultured lymphocytes (30).

Vinyl acetate is a vinyl ester. As a group, such esters should all be hydrolyzed in a similar way, yielding acetaldehyde. Filov’s (13) results suggest that at least vinyl formate, vinyl propionate, and vinyl butyrate are hydrolyzed to acetaldehyde, with vinyl formate hydrolysis occurring spontaneously in aqueous solution. Several vinyl esters were also found to be substrates for porcine pancreatic lipase (24). Thus the production of acetaldehyde may be an important metabolic activation reaction for a number of compounds.

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