Lack of Miscoding Properties of 7-(2-Oxoethyl)guanine, the Major Vinyl Chloride-DNA Adduct

Alain Barbin, Reinhold J. Laib1 and Helmut Bartsch2

International Agency for Research on Cancer, Division of Environmental Carcinogenesis, 150 Cours Albert Thomas, F 69372, Lyon Cedex 08, France [A. B., H. B.], and Institut für Arbeitsphysiologie an der Universität Dortmund, Ardeystrasse 67, D 4600 Dortmund, Federal Republic of Germany [R. J. L.]

ABSTRACT

Chloroethylene oxide, an ultimate carcinogenic metabolite of vinyl chloride, was reacted with poly(deoxyguanylate-deoxycytidylate); the nucleic acid base adducts, 7-(2-oxoethyl)guanine and 3,N4-ethenocytosine, were analyzed by reverse-phase high-performance liquid chromatography. Chloroethylene oxide-modified poly(deoxyguanylate-deoxycytidylate) was assayed as template in a replication fidelity assay with Escherichia coli DNA polymerase I, and the newly synthesized product was subjected to nearest-neighbor analysis. Misincorporation rates of deoxyadenosine monophosphate and thymidine monophosphate were found to increase with the level of template modification. About 80% of the mispairing events were located opposite minor cytokine lesions. 7-(2-Oxoethyl)guanine, the major adduct identified (>98% of the adducts), did not miscode for either thymine or adenine, failing to support an earlier hypothesis that the cyclic hemiacetal form, O6,7-(1'-hydroxyethano)guanine, could, by analogy with O6-alkylguanine, simulate adenine. Our results indicate that direct miscoding of 7-(2-oxoethyl)guanine may contribute only slightly to the induction of mutations by chloroethylene oxide or vinyl chloride.

INTRODUCTION

The mutagenic and carcinogenic activity (4, 9, 15) of vinyl chloride has been shown to be dependent upon its metabolic activation into CEO (Ref. 3; for a recent review, see Ref. 12). The carcinogenicity of CEO was demonstrated in mice (27), but no evidence has been obtained to date that chloroaetaodehyde, a rearrangement product (3), is carcinogenic (6, 26, 27).

CEO and chloroaetaodehyde can both bind covalently to nucleic acid bases in vitro to yield 1,N4-ethenoadenine, 3,C, and 3,N4-ethenocytosine (21). In a microsome-mediated assay, addition of vinyl chloride led to the formation in DNA of oxet-G, 1,N4-ethenoadenine, and 1,C. After rats were exposed for 2 years to vinyl chloride, 1,N4-ethenadoenine and 1,C were reported to have been formed in DNA (5); however, following shorter exposures to vinyl chloride, oxet-G was found to be the major DNA adduct formed in rats (13, 14) and mice (19).

By analogy to the promutagenic lesion O6-alkylguan (22), it was suggested that the genetic and possibly carcinogenic effects of vinyl chloride might result from the persistence of miscoding DNA adducts (3, 16, 21, 27). Previous reports (2, 7, 23, 25) indicated a slightly decreased fidelity of replication of synthetic polynucleotides with Escherichia coli DNA polymerase I, when the templates contained 1,N4-ethenoadenine or 3,C. As an extension of these studies, we have now investigated the coding properties of oxet-G, which has been proposed to miscode for thymine, forming the formation of a cyclic hemiacetal at the O6-position (Ref. 21; see Chart 1).

MATERIALS AND METHODS

Treatment of Templates

Poly(dG-dC) [dG, = 8.0, 20.3 A350 units/mg, from P-L Biochemicals GmbH, St. Goar, Federal Republic of Germany] was prepared by dissolving 4.35 mg in 14.5 ml 50 mM sodium cacodylate buffer (pH 7.0):0.2 M sodium chloride. CEO [purity >99.5%, prepared and stored as described previously (3)] in 1- to 5-μl aliquots was added under constant stirring at room temperature (21°C). A pH of 7.0 was maintained carefully by addition of 2 M NaOH using an autoburet and an automatic titrator. Under these conditions, CEO reacted very rapidly (half-life, about 3 min). At the end of the reaction, after each addition, was indicated by a stable pH; another CEO aliquot was then immediately added and the pH was stabilized again. This operation was repeated until the desired CEO:nucleotide phosphorus ratio, i.e., 12, was attained. A 1.8-μl aliquot of the reaction medium was collected and stored at −70°C. Addition to the remaining poly(dG-dC) solution of CEO was continued as described above, until the CEO added:nucleotide phosphorus ratio was 45; a further 1.8-μl aliquot of the reaction medium was then collected and stored at −70°C. These operations were continued for further modification of the polynucleotide. The 1.8-μl aliquots of the reaction medium thawed and passed through a Sephadex G-50F column (1 x 35.5 cm; Pharmacia Fine Chemicals, Uppsala, Sweden) with water as eluant, in order to remove salts and excess chloroaetaodehyde. Polymer-containing fractions were lyophilized; each batch of treated poly(dG-dC) was dissolved in 50 mM Tris-HCl buffer (pH 7.8) and stored at −20°C. The following CEO:nucleotide phosphorus molar ratios were used to modify the templates: 12, 45, 89, 173, 206, 256, 291, and 318; the treated templates are referred to, respectively, as T, III, IV, V, VI, VII, and VIII (Table 1). In some experiments, Templates VI, VII, and VIII were pooled; this pooled template is referred to as Template IX. Untreated poly(dG-dC) [control poly(dG-dC)] was processed in the same way as were the CEO-modified templates.

HPLC Techniques

HPLC separations were performed on a DuPont 850 liquid chromatograph (DuPont de Nemours S.A., Les Ulis, France); using a Hewlett-Packard 3390 A integrator (Hewlett-Packard, Orsay, France), UV absorbance was monitored at 254 nm. Mobile phases were prepared with Milli-Q water (Millipore water purification system); methanol (LChromsol, HPLC grade) and other chemicals (all analytical reagent grade) were obtained from Merck AG, Darmstadt, Federal Republic of Germany.

Analysis of CEO-treated Poly(dG-dC). Aliquots containing 100 μg CEO-treated poly(dG-dC) were lyophilized and subjected to acid or

1 Part of this work was performed under an IARC Research Training Fellowship at the International Agency for Research on Cancer, Lyon, France.
2 To whom requests for reprints should be addressed.
3 The abbreviations used are: CEO, chloroethylene oxide; oxet-G, 7-(2-oxoethyl)guanine; C, 3,N4-ethenocytosine; HPLC, high-performance liquid chromatography; poly(dG-dC), poly(deoxyguanylate-deoxycytidylate); AP, apurinic-apyrimidinic.
Received 12/13/83; revised 8/14/84, 12/11/84; accepted 2/21/85.
EFFECTS OF CEO-INDUCED LESIONS ON DNA REPLICATION

![Diagram of oxet-G and hemiacetal (II)]

**Chart 1.** Hypothesized misconding properties of oxet-G. Proposed equilibrium between oxet-G (I) and the hemiacetal (II) and mispairing scheme of II with thymine (III) (21). dR, deoxyribose.

Enzymic hydrolysis. The former was performed in 200 μl 0.1 n hydrochloric acid (45 min, 75°C), and samples were analyzed by HPLC without further treatment. For enzymic hydrolysis, samples were dissolved in chloric acid (45 min, 75°C), and samples were analyzed by HPLC without (III) (21). dR, deoxyribose.

(10 ¿»g, 0.06 unit) acid phosphatase (EC 3.1.3.2; Boehringer Mannheim) 200 nM 0.1 N hydrochloric acid (45 min, 75°C), and samples were analyzed by HPLC without (III) (21). dR, deoxyribose.

Enzymatic hydrolysis. The former was performed in 200 μl 0.1 n hydrochloric acid (45 min, 75°C), and samples were dissolved in chloric acid (45 min, 75°C), and samples were analyzed by HPLC without further treatment. For enzymic hydrolysis, samples were dissolved in chloric acid (45 min, 75°C), and samples were analyzed by HPLC without (III) (21). dR, deoxyribose.

Enzymatic hydrolysis. The former was performed in 200 μl 0.1 n hydrochloric acid (45 min, 75°C), and samples were dissolved in chloric acid (45 min, 75°C), and samples were analyzed by HPLC without further treatment. For enzymic hydrolysis, samples were dissolved in chloric acid (45 min, 75°C), and samples were analyzed by HPLC without (III) (21). dR, deoxyribose.

Nearest-Neighbor Analysis

Template Mixture IX was used for nearest-neighbor analysis and for nicking by an AP endonuclease.

Replication Fidelity Assays

Each reaction mixture (170 μl) contained 12.5 nmol untreated or CEO-treated poly(dG-dC) (nucleotide phosphorus); 400 pmol each of [8-3H]- dGTP (185 dpm/pmol), dCTP, dATP, or dTTP, 5'-α-32P]dATP (12,300 dpm/pmol), or 5'-α-32P]dATP (17,800 dpm/pmol) (free nucleoside 5' triphosphates were obtained from P-L Biochemicals; radioabeled nucleotides were from Amersham France, Versailles, France), and DNA was precipitated in cold 5% (w/v) trichloroacetic acid. The filters were rinsed 3 times in cold 5% trichloroacetic acid containing 2% (w/v) sodium pyrophosphate, twice in 5% trichloroacetic acid alone, and once in ethanol; the radioactivity present on the filters was determined by scintillation counting using Aquasol 2 (NEN Chemicals GmbH, Dreieich, Federal Republic of Germany).

Purification of the Replicated Templates. After 1 h incubation at 30°C, the polynucleotides were purified from excess nucleotides on Eutip-d columns (Schleicher & Schuell GmbH, Dassel, Federal Republic of Germany). Samples were charged on the columns and washed repeatedly with a low-salt solution [0.2 mM sodium chloride:1 mM EDTA:20 mM Tris-HCl buffer (pH 7.3 to 7.5)]. Templates were then eluted in a high-salt solution [1 mM sodium chloride:1 mM EDTA:20 mM Tris-HCl buffer (pH 7.3 to 7.5)], desalted on Sephadex G-50F (same conditions as under "Treatment of Templates"), and lyophilized.

Enzymatic Hydrolysis (10). Each of the 4 templates (control template and Template IX labeled with 5'-α-32P]dAMP or with 5'-α-32P]dTMP (13 to 25 μg) was dissolved in 975 mM 5 mivi Tris-HCl buffer (pH 8.6) with 2 mM calcium chloride. Micrococcal endonuclease (EC 3.1.16.1; Boehringer Mannheim) were added, and the mixture was nicked by an AP endonuclease.

After 2 h at 37°C, the mixtures were heated at 50°C.

**Analysis of Nucleotides.** Nucleotides were resolved by anion-exchange chromatography on a MicroPak AX-10 column (4 mm x 30 cm; Varian, Saint Priest, France). The gradient consisted of Eluant A (pH 7.3 to 7.5), desalted on Sephadex G-50F (same conditions as under "Treatment of Templates"), and lyophilized.

Enzymatic hydrolysis. The former was performed in 200 μl 0.1 n hydrochloric acid (45 min, 75°C), and samples were dissolved in chloric acid (45 min, 75°C), and samples were analyzed by HPLC without further treatment. For enzymic hydrolysis, samples were dissolved in chloric acid (45 min, 75°C), and samples were analyzed by HPLC without (III) (21). dR, deoxyribose.

**Nearest-Neighbor Analysis**

Template Mixture IX was used for nearest-neighbor analysis and for nicking by an AP endonuclease.

**Replication Fidelity Assays**

Each reaction mixture (170 μl) contained 12.5 nmol untreated or CEO-treated poly(dG-dC) (nucleotide phosphorus); 400 pmol each of [8-3H]-dGTP (185 dpm/pmol), dCTP, dATP, or dTTP, 5'-α-32P]dATP (12,300 dpm/pmol), or 5'-α-32P]dATP (17,800 dpm/pmol) (free nucleoside 5'-triphosphates were obtained from P-L Biochemicals; radioabeled nucleotides were from Amersham France, Versailles, France), and DNA was precipitated in cold 5% (w/v) trichloroacetic acid. The filters were rinsed 3 times in cold 5% trichloroacetic acid containing 2% (w/v) sodium pyrophosphate, twice in 5% trichloroacetic acid alone, and once in ethanol; the radioactivity present on the filters was determined by scintillation counting using Aquasol 2 (NEN Chemicals GmbH, Dreieich, Federal Republic of Germany).

**Purification of the Replicated Templates.** After 1 h incubation at 30°C, the polynucleotides were purified from excess nucleotides on Eutip-d columns (Schleicher & Schuell GmbH, Dassel, Federal Republic of Germany). Samples were charged on the columns and washed repeatedly with a low-salt solution (0.2 mM sodium chloride:1 mM EDTA:20 mM Tris-HCl buffer (pH 7.3 to 7.5)). Templates were then eluted in a high-salt solution (1 mM sodium chloride:1 mM EDTA:20 mM Tris-HCl buffer (pH 7.3 to 7.5)), desalted on Sephadex G-50F (same conditions as under "Treatment of Templates"), and lyophilized.

Enzymatic Hydrolysis (10). Each of the 4 templates (control template and Template IX labeled with 5'-α-32P]dAMP or with 5'-α-32P]dTMP (13 to 25 μg) was dissolved in 975 mM 5 mivi Tris-HCl buffer (pH 8.6) with 2 mM calcium chloride. Micrococcal endonuclease (EC 3.1.16.1; Boehringer Mannheim) were added, and the mixture was nicked by an AP endonuclease.

After 2 h at 37°C, the mixtures were heated at 50°C.

**Determination of the Specific Activities of 3'-dCMP and 3'-dGMP.** Enzymatic hydrolysates were brought to pH 2.3 by the addition of dilute hydrochloric acid, 50 μg (0.1 unit) calf spleen phosphodiesterase (EC 3.1.16.1; Boehringer Mannheim) were added, and the mixture was incubated at 37°C. At the end of 1 h, the same amount of enzyme was added, and incubation was continued for another 2 h.

**Nicking of AP Sites**

*Micrococcus luteus* AP endonuclease B (a generous gift from Drs. J. P. Pierre and J. Laval, Institut Gustave Roussy, Villejuif, France) was used to nick phosphodiester bonds at AP sites (20). The reaction mixture (110 μl) contained 50 mM Tris-HCl buffer (pH 8.0), 2.5 mM magnesium chloride, 6.25 nmol poly(dG-dC) (nucleotide phosphorus), and 1 or 2 units AP endonuclease B. After 2 h at 37°C, the mixtures were heated at 50°C.
for 3 min. Controls were processed in the same way but without AP endonuclease.

For replication fidelity assays, 400 pmol (in 10 μl Tris-HCl buffer) each of [3H]dGTP [185 dpm/pmol], dCTP, dATP, or dTTP. [32P]dTTP [5800 dpm/pmol], or [32P]dATP [9800 dpm/pmol] and 2 units E. coli DNA polymerase I [in 23 μl 50 mM Tris-HCl (pH 7.8); 40 mM magnesium chloride] were added, and incubation was carried out for 1 h at 30°C. Radioactivity incorporated into DNA was measured as described under "Replication Fidelity Assays."

RESULTS

HPLC Analysis of Nucleobase Adducts in CEO-treated Poly(dG-dC). Treatment of poly(dG-dC) (double-stranded form) with increasing concentrations of CEO resulted in the dose-dependent formation of oxet-G as the main alkylation product in poly(dG-dC) (Table 1, Column 2). Only trace amounts of 3',4'-ethenodeoxycytidine were formed after treatment with the highest concentrations of CEO (Templates VI, VII, VIII; Table 1, Column 3). N2,3-Ethenoguanine could not be detected.

Misincorporation of dTMP and dAMP in CEO-treated Poly(dG-dC) Templates. When poly(dG-dC) templates containing increasing amounts of oxet-G and C were incubated in the presence of E. coli DNA polymerase I and the 4 deoxyribonucleoside 5'-triphosphates, the rate of replication decreased, and the frequencies of dAMP and dTTP incorporation increased (Table 1, Columns 4, 5, and 6).

Nearest-Neighbor Analysis of Replicated Templates. In order to determine the sites of misincorporation of dAMP and dTMP in the presence of [3H]dGTP and either [32P]dATP, or [32P]dTTP and the 3 other nucleotides (Table 1). Following incubation, the templates were purified, hydrolyzed to nucleoside 3'-monophosphates, and analyzed by HPLC and scintillation counting (Table 2). A major part of adenine was incorporated opposite guanine, whereas thymine was distributed equally opposite cytosine and guanine; the 2 distributions varied by only 4 to 5% from one template to the other (Table 2, Columns 4 and 7). The contributions of cytosine and guanine lesions to the misincorporation events were evaluated by their mispair frequencies (Table 2, Columns 5 and 8) calculated as error rate (Table 1, Columns 5 and 6) multiplied by the fraction of CpY or GpY sequences (Table 2, Columns 4 and 7; Y stands for A or T). The frequencies of mispairings induced by CEO treatment were calculated by subtracting the background frequencies (Table 2, Column 5) from the frequencies observed with Template IX (Table 2, Column 8): C:A, 13.2 x 10^-3; G:A, 3.3 x 10^-3; C:T, 0.9 x 10^-3; G:T, 1 x 10^-3. Thus, 80% of the CEO-induced dAMP incorporation occurred opposite cytosine residues; but the proportions of new C:T and G:T mismatches were roughly equal. The contributions of cytosine and guanine lesions to the overall dAMP and dTMP misincorporations induced by CEO treatment were 77 and 23%, respectively; therefore, cytosine lesions were about 3 times more efficient than were guanine lesions in decreasing the fidelity of DNA synthesis.

Misincorporation of dAMP and dTMP following Nicking of AP Sites. In order to assess the role of AP sites in the replication errors observed with CEO-treated poly(dG-dC), Template IX was nicked with M. luteus AP endonuclease B and replicated by E. coli DNA polymerase in the presence of the 4 deoxyribonucleoside 5'-triphosphates, including [3H]dGTP and either [32P]dATP, or [32P]dTTP. After Template IX had been nicked by an AP endonuclease, the efficiency of DNA synthesis was enhanced. Taking the rate of replication of control poly(dG-dC) as 100% (see Table 1), the efficiency of replication of Template IX was 83 ± 0.14.

### Table 1

CEO-modified poly(dG-dC) templates: HPLC analysis and misincorporation assays

<table>
<thead>
<tr>
<th>Template</th>
<th>Oxet-G:guanine</th>
<th>C:cytosine</th>
<th>dAMP incorporation (pmol)</th>
<th>dTMP:dGMP</th>
<th>dAMP:dGMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(dG-dC)</td>
<td>0</td>
<td>0</td>
<td>12.8 ± 12.6</td>
<td>8.8</td>
<td>12</td>
</tr>
<tr>
<td>I</td>
<td>0.014 ± 0.002</td>
<td>ND</td>
<td>48.2 ± 5.3</td>
<td>4.0</td>
<td>13</td>
</tr>
<tr>
<td>II</td>
<td>0.047 ± 0.002</td>
<td>ND</td>
<td>22.8 ± 2.6</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>III</td>
<td>0.123 ± 0.006</td>
<td>ND</td>
<td>33.2 ± 1.7</td>
<td>8.7</td>
<td>57</td>
</tr>
<tr>
<td>IV</td>
<td>0.185 ± 0.005</td>
<td>ND</td>
<td>12.5 ± 1.6</td>
<td>7.3</td>
<td>57</td>
</tr>
<tr>
<td>V</td>
<td>0.290 ± 0.012</td>
<td>ND</td>
<td>11.6 ± 1.6</td>
<td>16</td>
<td>98</td>
</tr>
<tr>
<td>VI</td>
<td>0.337 ± 0.009</td>
<td>0.0025</td>
<td>3.29 ± 0.35</td>
<td>24</td>
<td>150</td>
</tr>
<tr>
<td>VII</td>
<td>0.381 ± 0.007</td>
<td>0.0005</td>
<td>4.35 ± 0.16</td>
<td>29</td>
<td>180</td>
</tr>
<tr>
<td>VIII</td>
<td>0.361 ± 0.012</td>
<td>0.0005</td>
<td>3.02 ± 0.60</td>
<td>32</td>
<td>200</td>
</tr>
<tr>
<td>IX</td>
<td>0.360</td>
<td>0.005</td>
<td>3.33</td>
<td>28</td>
<td>177</td>
</tr>
</tbody>
</table>

* Roman numerals refer to poly(dG-dC) treated with various amounts of CEO.

* Molar ratio, oxet-G determined by HPLC, following acid hydrolysis.

* Molar ratio, determined as nucleosides by HPLC, following enzymatic hydrolysis.

* Expressed as the noncomplementary:complementary nucleotide molar ratio incorporated on the templates.

* Mean ± SD; n = 3.

* ND, not detected.

* Mixture of equimolar amounts of Templates VII, VIII, and IX. These templates were pooled in order to facilitate nearest-neighbor analyses (see Table 2). Composition, replication rate, and error rates were calculated as the means of the corresponding values observed with Templates VII, VIII, and IX.

Cancer Res. 1985;45:2442-2453.
was 3%; it was 12% following incubation with 1 unit of AP endonuclease and 20% when 2 units of enzyme were used.

The error rates of dTMP:dGMP and dAMP:dGMP were decreased by factors of 1.7 and 2.4, respectively, after incubation of Template IX with 2 units of endonuclease. There were different effects on dAMP incorporation and replication rate; the replication rate was doubled when 2 units of enzyme were used instead of 1, but there was no further (or only a marginal) reduction in the dAMP:dGMP ratio.

**DISCUSSION**

In HPLC analyses, following the reaction of CEO with poly(dG-dC) in a double-stranded form (Table 1), oxet-G amounted to >98% of the total adducts identified. This finding is consistent with those obtained by analysis of liver DNA from vinyl chloride-treated rodents (13, 14, 19). N7,3'-Ethenoguanine and C may be formed from chloroacetaldehyde or CEO (1, 11, 13, 16); the former adduct was not detected in our templates, and only minute amounts of C were formed at the highest concentrations of CEO. The presence of the hydrated intermediate of C, a nonmiscoding adduct (25), was not investigated. This differential alkylation by CEO of guanine and cytosine moieties in double-stranded DNA is consistent with its nucleophilic selectivity (Swain-Scott's constant, s = 0.83 (8)); by comparison with methyl methanesulfonate, which has a similar selectivity, CEO:cytosine adducts would be expected to comprise <1% of the CEO:guanine adducts (22).

It has been proposed that oxet-G is in equilibrium with a cyclic hemiacetal form, O(7)-3'-hydroxyethano)guanine, after reaction of the 7-(2-oxoethyl) group with the O(7)-position, and that this form could, by analogy with O(7)-methylguanine (22), miscode for thymine (Ref. 21; Chart 1). In order to test this hypothesis, we performed misincorporation assays with CEO-treated poly(dG-dC) templates and E. coli DNA polymerase I. Because O(7)-3'-hydroxyethano)guanine may represent only a small proportion of the total oxet-G residues, we used also highly modified templates containing up to 27% of oxet-G residues (Table 1). dTMP incorporation was enhanced only after treatment of poly(dG-dC) with high concentrations of CEO, failing to support the above hypothesis.

Although an increase in dAMP incorporation was observed with all the CEO-treated templates, nearest-neighbor analysis (Table 2) demonstrated that lesions mainly at cytosine sites were involved. Data from the misincorporation assays and from nearest-neighbor analyses show that at most 0.4 and 1.2% of the oxet-G moieties would mispair with thymine and adenine, respectively. Furthermore, about one-half of the dAMP and dTMP misincorporations may be due to AP sites, as shown by the effect of AP endonuclease treatment on the replication rate and on the error rates.

Our results indicate, therefore, that direct miscoding of oxet-G may not contribute greatly to the induction of mutagenicity by CEO or vinyl chloride. Investigations are in progress to evaluate the possible role of minor vinyl chloride:DNA adducts (1, 13, 17, 18, 24).

**ACKNOWLEDGMENTS**

We wish to thank Dr. A. Croisy (Institut Curie, Orsay, France) for the preparation of CEO, Drs. J. Pierre and J. Leval (Institut Gustave Roussy, Villejuif, France) for the kind gift of AP endonuclease B, and J-C. Béreliaz for skilful technical assistance. We are indebted to M. Wrisz for typing the manuscript and to E. Heseltine for editorial assistance.

**REFERENCES**

6. Gwinner, L. M., Lab, R. J., Fiser, J. G., and Bolt, H. M. Evidence of chloroth-
Effects of CEO-Induced Lesions on DNA Replication

Vinyl chloride being the reactive metabolite of vinyl chloride towards DNA: comparative studies with 2,2'-dichlorodiethylene. Carcinogenesis (Lond.), 4: 1483-1486, 1983.


Lack of Miscoding Properties of 7-(2-Oxoethyl)guanine, the Major Vinyl Chloride-DNA Adduct

Alain Barbin, Reinhold J. Laib and Helmut Bartsch

*Cancer Res* 1985;45:2440-2444.

Updated version  Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/45/6/2440

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.