EARLY EVENTS IN THE INDUCTION OF RAT HEPATIC UDP-GLUCURONOSYLTRANSFERASES, GLUTATHIONE S-TRANSFERASE, AND MICROSOMAL EPOXIDE HYDROLASE BY 1,7-PHENANTHROLINE: COMPARISON WITH OLTIPRAZ, TERT-BUTYL-4-HYDROXYANISOLE, AND TERT-BUTYLHYDROQUINONE

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ABSTRACT:

Several classes of compounds are able to induce a spectrum of drug-metabolizing enzymes without inducing cytochrome P450s. Examples include antioxidants such as tert-butyl-4-hydroxyanisole and its metabolite tert-butylhydroquinone, dithiolthiones such as oltipraz, and N-heterocycles such as 1,7-phenanthroline. The events associated with induction of UDP-glucuronosyltransferases (UGT), glutathione S-transferases, and microsomal epoxide hydrolase after a single oral dose of these agents have been compared. No agent significantly elevated any of these enzyme activities within 24 h, but oltipraz and 1,7-phenanthroline significantly increased glutathione S-transferase and UGT activities by 48 h. 1,7-Phenanthroline and oltipraz showed generally similar time-course responses of drug-metabolizing enzyme mRNAs; little change from control at 6 h followed by significant and maximal increases 12 to 18 h after treatment. Maximal mRNA changes for 1,7-phenanthroline and oltipraz were of similar magnitude and clustered around 4-fold for most enzymes. With the exception of one UGT isozyme (UGT1A1), the elevations in mRNA were blocked by prior administration of actinomycin D, indicative of a transcription-dependent response. Neither tert-butyl-4-hydroxyanisole nor tert-butylhydroquinone caused a statistically significant increase in any mRNA examined at any time point.

The liver contains an abundance of enzymes that are responsible for the metabolism of xenobiotic compounds. Reactions involved in xenobiotic metabolism are often classified by the generalized functional outcome. With this classification, cytochrome P450-catalyzed oxidations are most often considered as (bio)activating reactions, whereas the reactions catalyzed by epoxide hydrolases and conjugations are considered as detoxication reactions. Two major classes of enzymes catalyzing conjugations include UDP-glucuronosyltransferases (UGT) and glutathione S-transferases (GST). The relative abundance of enzymes catalyzing the two categories of reactions can be of importance because of the toxicities that can arise when the balance between activation and detoxication reactions is altered. Agents that induce cytochrome P450 often also elicit a response in detoxication enzymes, but the responses may not occur equally, and the balance may lean toward activation. However, some agents selectively induce enzymes involved in detoxication reactions and therefore have the potential to prevent against chemical carcinogenesis (Wattenberg, 1985; Talalay et al., 1988) because the mutagenic effects of carcinogens are often mediated through an excess of cytochrome P450-generated reactive intermediates.

Oltipraz has been extensively investigated for its ability to preferentially induce enzymes that catalyze detoxifying reactions. It contains a 1,2-dithiol motif that appears essential for both its induction properties and its ability to ameliorate aflatoxin B1-induced hepatocarcinogenesis (Kensler et al., 1987; Egner et al., 1994; Maxuitenko et al., 1996). Dietary administration of oltipraz increases hepatic UGT, microsomal epoxide hydrolase (mEH), and GST enzyme activities and mRNAs (Ansher et al., 1986; Kensler et al., 1987; Buetler et al., 1995) to a greater extent than cytochrome P450 concentration (Kensler et al., 1987) and CYP1A1, CYP1A2, CYP2B, and CYP3A mRNAs in rat liver (Buetler et al., 1995; Kessler and Ritter, 1997). For many detoxifying enzymes, there is considerable evidence that the oltipraz-mediated induction arises from an increase in transcription (Davidson et al., 1990; Clapper et al., 1994; Egner et al., 1994; Bueter et al., 1995; Metz and Ritter, 1998).

Another class of compounds able to selectively induce enzymes involved in performing detoxication reactions are simple aromatic compounds containing one or more nitrogen heteroatom(s), a group which includes certain phenylpyridines, dipyrldyls, quinolines, phenanthrolines, and benzoquinolines (Franklin, 1991; Franklin and Moody, 1992; Franklin et al., 1993; Le et al., 1997; Le and Franklin, 1997). Thus 1,7-phenanthroline, for example, induces UGT, GST, and mEH enzyme activities without inducing cytochrome P450 isozymes (Franklin et al., 1993). These N-heterocycles lack the 1,2-dithiol motif of oltipraz. After multiple daily doses, mRNAs as well as enzyme activities are elevated (Vargas et al., 1998), but whether this is a...
primary response or a response secondary to any physiological effects of multiple doses is not known. The present study investigates the initial events leading to these increases by examining the early events following a single dose of a N-heterocycle-containing compound. It examines the coordinate induction of multiple drug-metabolizing enzymes by 1,7-phenanthroline in rat and compares them with changes elicited by the similar doses of oltipraz, tert-butyl-4-hydroxyanisole (BHA), and a major metabolite, tert-butylhydroquinone (BHQ), for the same enzymes. Prior treatment with actinomycin D is used to delineate induction responses that result from DNA-dependent mRNA synthesis.

Materials and Methods

Chemicals. Oltipraz was synthesized by Rhone Poulenc Rorer (Evry, France), 1,7-phenanthroline and BHQ were purchased from Aldrich (St. Louis, MO), phenobarbital was purchased from Ganes Chemical Works (New York, NY), and morphine sulfate was purchased from Merck and Co. Inc. (Rahway, NJ). Actinomycin D, BHA, and all other biochemicals were purchased from Sigma Chemical Co. (St. Louis, MO). TRIZol solution for total RNA isolation was purchased from Life Technologies (Grand Island, NY). Nytran membranes were purchased from Schleicher and Schuell (Keene, NH), and the Multiprime DNA labeling kit was purchased from Amersham Pharmacia Biotech (Little Chalfont, UK). [α-32P]dCTP was purchased from DuPont NEN (Boston, MA).

Animals and Treatment. Adult male Sprague-Dawley rats (125–275 g) were maintained under a 12-h light/dark cycle in a temperature- and humidity-controlled environment with free access to food and water. Inducers were all administered by the intragastric (i.g.) route. Treatments were BHA and BHQ (75 mg/kg in corn oil vehicle), oltipraz (75 or 100 mg/kg in 0.5% methylcellulose suspension), and 1,7-phenanthroline (75 mg/kg either solubilized in molar equivalent HCl solution or suspended in 0.5% methylcellulose). Phenobarbital (100 mg/kg in a 0.5% methylcellulose suspension) was given by the i.g. route. Actinomycin D was administered by the i.p. route at 2 mg/kg 1 h before the inducing agents.

Liver Drug-Metabolizing Enzymes. Drug-metabolizing enzyme activities were determined in microsomal and cytosol fractions separated by differential centrifugation and calculated based on the protein concentration. Protein concentration, cytosolic GST activity, microsomal cytochrome P450 concentration, and UGT activities toward 4-nitrophenol, 1-naphthol, and morphine were determined as referenced elsewhere (Le and Franklin, 1997).

Northern Blot Analysis. The cDNA probes used were as described in Vargas et al. (1997), except for UGT1A1, which was newly prepared using reverse transcription-polymerase chain reaction with primers –2 to +18 (5' sense) and +868 to +849 (3' antisense) of the cDNA for UGT1A1 (GenBank accession no. U20551). The 870-base pair fragment was subcloned into pBluescript SK (+/−). Northern blots were performed with 20 μg of total RNA per lane. RNA was isolated from 100 mg of liver using Trizol extraction. Hybridized blots were washed twice for 30 min at 42°C in 2× standard saline citrate (SSC), 0.1% SDS, twice for 30 min at 42°C in 0.1× SSC, 0.1% SDS, and once for 45 min at 54°C in 0.1× SSC, 0.1% SDS. Autoradiographic film was exposed for 6 to 72 h at −70°C with an intensifying screen, and the developed band intensity was determined by scanning densitometry using Molecular Analyst software (Bio-Rad, Hercules, CA). All mRNA bands were normalized to the same-sample cyclophilin mRNA band to control for gel loading and transfer variations.

Statistical Analysis. All values were obtained from sample groups of at least three different animals. Statistical analyses were performed using ANOVA, followed by Fisher’s protected least significant difference multiple range test. Differences were considered significant at P values of <.05.

Results

The magnitude and timing of hepatic drug-metabolizing enzyme changes after a single dose of three classes of agents known to be selective inducing agents after multiple administration or after chronic or dietary exposure have been investigated. When 1,7-phenanthroline and oltipraz were examined, the spectrum of enzyme activities affected was identical with that seen with studies using a multiple daily dose schedule. GST and multiple UGT activities (4-nitrophenol, 1-naphthol, morphine) were increased without any increase in cytochrome P450 concentration (Table 1). The elevations in enzyme activities were clearly evident after a period of 48 h; intermediate increases at 24 h did not achieve statistical significance. A single dose of either BHA or BHQ did not elevate any enzyme activity by 24 h (data not shown), and because neither agent produced significant changes in mRNAs over the time course investigated (see below), they were not investigated for enzyme activity induction at the 48 h
The induction of GST-Ya mRNA by agents that preferentially induce detoxifying enzymes

Values are expressed as mean ± S.E., with n = 3–4.

<table>
<thead>
<tr>
<th>Inducing Agent</th>
<th>GST-Ya mRNA (% Zero-Time Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>100 ± 16</td>
</tr>
<tr>
<td>1,7-P (solution)</td>
<td>100 ± 11</td>
</tr>
<tr>
<td>1,7-P (suspension)</td>
<td>100 ± 16</td>
</tr>
<tr>
<td>Oltipraz (75 mg/kg)</td>
<td>100 ± 11</td>
</tr>
<tr>
<td>Oltipraz (100 mg/kg)</td>
<td>100 ± 16</td>
</tr>
<tr>
<td>BHA</td>
<td>100 ± 3</td>
</tr>
<tr>
<td>BHO</td>
<td>100 ± 13</td>
</tr>
</tbody>
</table>

<sup>a</sup> Significantly different (P < .05) from controls.

<sup>b</sup> Significantly different (P < .05) from solution formulation.

<sup>c</sup> Significantly different (P < .05) from 75 mg/kg.

time period. The increases after 1,7-phenanthroline and oltipraz, although differing in the pattern of enzyme activities induced, were of similar magnitude and time course to those elicited by phenobarbital, a prototype non(phase)-selective inducing agent.

The timing of the enzyme activity changes was compatible with induction by a transcriptional activation mechanism. Northern blotting was used to assess the mRNA changes for the detoxifying enzymes during the first 24 h. In addition, treatment with actinomycin D 1 h before inducing agent was used to confirm a transcriptional activation mechanism. For the cytosolic enzyme GST-Ya (Table 2), both 1,7-phenanthroline and oltipraz showed a mRNA time course characterized by little or only minimal increase by 6 h, a peak elevation between 12 and 18 h, and a return toward the control value thereafter. 1,7-Phenanthroline and oltipraz produced a greater response than the antioxidant BHA and its metabolite BHQ. Neither BHA nor BHQ elicited a significant change in GST-Ya mRNA at any time point investigated. The 12-h mRNA response was independent of whether the 1,7-phenanthroline was administered in soluble or suspension form, the suspension form providing the inducer in the same manner as oltipraz. However, the suspension form appeared to enhance the 18-h induction response. The 12-h change in GST-Ya mRNA elicited by the higher dose (100 mg/kg) of oltipraz (an equimolar dose to 75 mg/kg of 1,7-phenanthroline) was significantly higher than that elicited by an equigravimetric dose. Both the 1,7-phenanthroline and oltipraz 12-h mRNA elevations were completely blocked by actinomycin D.

For the microsomal detoxifying enzyme mEH, the mRNA increases were slightly higher than for GST-Ya, but the response was essentially similar in time course, enhanced 18-h response with suspension formulation (1,7-phenanthroline), absence of induction by BHA and BHQ, and the block of the 12-h responses to 1,7-phenanthroline and oltipraz by actinomycin D (Table 3). For mEH mRNA however, the 12-h changes elicited by the two doses of oltipraz were not significantly different from each other.

With only a minor deviation, the response of two other microsomal enzymes, UGT1A6 (Table 4) and UGT2B1 (Table 5) closely paralleled the GST-Ya response. The minor variation was seen in the 12-h UGT2B1 response to 1,7-phenanthroline where the suspension formulation caused a significantly greater response than the solubilized preparation, an outcome also seen with GST-Ya. Elevations in the mRNA of a third UGT isozyme, UGT1A1, were lesser in magnitude than for the other two examined (Table 6), and prior administration of actinomycin D did not appear to block this increase.

### Discussion

As important as the absolute amount of drug-metabolizing enzymes is the overall balance of the enzymes and reactions that activate and inactivate drugs and other xenobiotics. The up-regulation of drug-metabolizing enzymes to meet exposure demands often involves a battery of both activating and detoxication enzymes that are induced through a common mechanism. The genes for several drug-metabolizing enzymes, including CYP1A1, UGT1A6, GST-Ya, and quinone oxidoreductase, contain a xenobiotic response element enhancer that allows their coordinate induction by polycyclic aromatic hydrocarbons and related compounds (Rushmore et al., 1990; Favreau and Pickett, 1991; Hankinson, 1995; Emtia et al., 1996). Some of these same genes also contain an antioxidant/electrophile response element and so can also be transcriptionally activated by antioxidant compounds such as BHA and compounds having electrophilic properties. This cis-acting regulatory element is found in the promoter region of rat GST-Ya (Rushmore and Pickett, 1990) and quinone oxidoreductase (Favreau and Pickett, 1991) genes but appears to be absent from cytochrome P450s. Therefore, inducing agents acting through this mechanism have the potential for shifting the balance of xenobiotic activation/inactivating enzymes toward a state more likely to result in xenobiotic detoxication.

Oltipraz, a drug originally used for the treatment of schistosomiasis, has been found to protect against cancer in the lung, bladder, colon, liver, skin, and mammary gland in rodents (Ansher et al., 1986) and has undergone clinical investigation as a chemoprotectant compound (Jacobson et al., 1997; Zhang et al., 1997; Wang et al., 1999). Oltipraz also protects against the hepatotoxicity of acetaminophen, carbon tetrachloride (Ansher et al., 1983), and aflatoxin B1 in rodents (Kessler et al., 1987; Liu et al., 1988). The protection against these diverse agents has been largely attributed to the ability of oltipraz to preferentially induce detoxifying drug-metabolizing enzymes. Preferential rather than exclusive induction was demonstrated in a study where in addition to increasing UGT1A6 and UGT2B1 mRNAs, oltipraz also increased mRNAs of CYP1A1 and CYP2B (Grove et al., 1997; Kessler and Ritter, 1997).

Certain N-heterocyclic compounds induce UGT1A6- and GST-Ya-dependent enzyme activities in rat liver without the coinduction of any P450 isozymes (Franklin, 1991; Franklin and Moody, 1992; Franklin...
The present studies may reflect this large potency differential, a factor accommodated in comparative chronic dietary studies by a higher level of supplementation (e.g., 5-fold; Kensler et al., 1985). In the present study, there was no evidence that BHQ was any more or less effective than BHA. Less effective induction by BHQ would be in concurrence with chronic dietary induction studies in mice (Rahimtula et al., 1982), and no difference in induction between the two compounds would agree with the conclusion, also from chronic exposure studies in mice, reached by Prochaska et al. (1985).

The time course for mRNA changes after 1,7-phenanthroline and oltipraz, is characterized by significant and maximal increases between 12 and 18 h, and is compatible with the timing of a transcriptional activation mechanism. For 2-(allylthio)pyrazine, another potential chemoprotective compound, the maximal responses of five GST mRNAs and mEH mRNA was found to be 24 h after oral dosing (Kim et al., 1999). The uniformity of the refractory period before the time of maximal response suggests close parallels in the rate of absorption from the i.g. site of administration and distribution to the liver for both compounds and/or close parallels in the intracellular processes occurring before transcription. Also, if metabolism is required for induction (a supposition without basis at the present time), the similarity in the time course of response between the two compounds indicates that metabolism must be similarly rapid for the dithiolthione and the heterocycle. That BHQ was no more effective an inducing agent than BHA would also indicate that limitations in metabolism are not

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**TABLE 3**

The induction of mEH mRNA by agents able to preferentially induce detoxifying enzymes

<table>
<thead>
<tr>
<th>Inducing Agent</th>
<th>mEH mRNA (% Zero-Time Value)</th>
<th>0</th>
<th>6 h</th>
<th>12 h</th>
<th>12 h and actinOD</th>
<th>18 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>100 ± 23</td>
<td>55 ± 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,7-P (solution)</td>
<td>100 ± 14</td>
<td>155 ± 18</td>
<td>482 ± 106a</td>
<td></td>
<td>287 ± 46a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,7-P (suspension)</td>
<td>100 ± 23</td>
<td>471 ± 133a</td>
<td>104 ± 30</td>
<td>459 ± 141a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oltipraz (75 mg/kg)</td>
<td>100 ± 14</td>
<td>112 ± 16</td>
<td>392 ± 47a</td>
<td>421 ± 126a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oltipraz (100 mg/kg)</td>
<td>100 ± 23</td>
<td>429 ± 125a</td>
<td>136 ± 22</td>
<td>247 ± 134a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BHA</td>
<td>100 ± 23</td>
<td>87 ± 13</td>
<td>67 ± 1</td>
<td>58 ± 4</td>
<td>75 ± 4</td>
<td>98 ± 12</td>
<td></td>
</tr>
<tr>
<td>BHQ</td>
<td>100 ± 19</td>
<td>63 ± 11</td>
<td>113 ± 14</td>
<td>58 ± 17</td>
<td>75 ± 4</td>
<td>82 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

1,7-P, 1,7-phenanthroline; actinOD, actinomycin D. 2 mg/ml given 1 h before inducer.

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**TABLE 4**

The induction of UGT1A6 mRNA by agents able to preferentially induce detoxifying enzymes

<table>
<thead>
<tr>
<th>Inducing Agent</th>
<th>UGT1A6 mRNA (% Zero-Time Value)</th>
<th>0</th>
<th>6 h</th>
<th>12 h</th>
<th>12 h and actinOD</th>
<th>18 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>100 ± 4</td>
<td>105 ± 27</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1,7-P (solution)</td>
<td>100 ± 4</td>
<td>121 ± 5</td>
<td>545 ± 56a</td>
<td></td>
<td>306 ± 47a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,7-P (suspension)</td>
<td>100 ± 4</td>
<td>633 ± 134a</td>
<td>127 ± 34</td>
<td>889 ± 195a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oltipraz (75 mg/kg)</td>
<td>100 ± 4</td>
<td>175 ± 8</td>
<td>323 ± 23a</td>
<td>427 ± 54a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oltipraz (100 mg/kg)</td>
<td>100 ± 4</td>
<td>647 ± 140a,c</td>
<td>124 ± 23</td>
<td>320 ± 50a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BHA</td>
<td>100 ± 15</td>
<td>88 ± 13</td>
<td>93 ± 26</td>
<td>112 ± 11</td>
<td>129 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BHQ</td>
<td>100 ± 4</td>
<td>101 ± 7</td>
<td>191 ± 7</td>
<td>87 ± 14</td>
<td>152 ± 6</td>
<td>121 ± 12</td>
<td></td>
</tr>
</tbody>
</table>

1,7-P, 1,7-phenanthroline; actinOD, actinomycin D. 2 mg/ml given 1 h before inducer.

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et al., 1993; Le and Franklin, 1997). Similar to oltipraz, chronic or multiple dosing with 1,7-phenanthroline induced both UGT1A6 and UGT2B1, detoxifying enzymes classically induced by different mechanisms by 3-methylcholanthrene and phenobarbital, respectively (Iyanagi et al., 1986; Mackenzie, 1986). The lack of concomitant induction of CYP1A1 with UGT1A6 in these studies argues against a xenobiotic response-element-mediated mechanism contributing to induction by 1,7-phenanthroline.

The mRNA changes of several drug-metabolizing enzymes after a single dose of 1,7-phenanthroline and oltipraz revealed a generally similar time course for all enzymes, a period after treatment (0–6 h) during which there was little or no statistical change from controls followed by a large, significant, and peaking increase over the next 6 to 12 h. In contrast to 1,7-phenanthroline and oltipraz, single doses of either BHA or BHQ did not cause major increases in the mRNAs of any of the detoxication enzymes examined. The present studies may appear to conflict with prior studies where, when included in the diet (0.5 to 0.75%), antioxidants such as BHA induce GST-Ya and UGT1A6 mRNAs (Kashfi et al., 1994; Buetler et al., 1995) in rat liver. However, it should be noted that for a mature rat consuming up to 20 g of food per day (Strohmayer et al., 1980), BHA supplementation at 0.75% provides a daily dose of approximately up to 600 mg/kg, and therefore induction by phenolic antioxidants may require heroic doses. The present studies may reflect this large potency
the explanation for the lack of induction by BHA. The postmaximum decline in mRNAs suggests a lack of continued presence of the oltipraz within the liver, an expectation not altogether unrealistic given that the plasma half-life of oltipraz is less than 6 h in rodents (Heusse et al., 1985). For 1,7-phenanthroline, the postmaximum decline in mRNAs was influenced by the vehicle used for administration. Administration in methycellulose suspension did not significantly alter the magnitude of the 12-h response, but the response seen after 18 h was significantly higher than after administration in soluble form, probably as a result of a more sustained absorption from the gastrointestinal tract.

The generally parallel nature of the mRNA responses to 1,7-phenanthroline and oltipraz after single oral dose administration could be construed as suggestive of a common mechanism. For oltipraz induction of GST, there is evidence that transcriptional initiation via the antioxidant/electrophile response element contributes to the induction seen within 24 h of dietary oltipraz exposure (Davidson et al., 1990). The possibility of a different mechanism for 1,7-phenanthroline could be entertained because 1,7-phenanthroline lacks the 1,2-dithiol motif that in structure activity relationship studies was critical for the induction of detoxifying enzymes and amelioration of aflatoxin B1 liver toxicity. However, elimination of mRNA increases by prior treatment with actinomycin D firmly indicates a transcriptional response to 1,7-phenanthroline, an effect also reproduced for oltipraz. The induction of UGT1A1 mRNA by both 1,7-phenanthroline and oltipraz was not significantly depressed by prior actinomycin D administration. Whether the low magnitude of UGT1A1 induction is the reason for the lack of statistical significance or whether there is indeed a different mechanism of induction for this UGT isozyme (e.g., mRNA stabilization) remains to be established.

The selected N-heterocyclic compound investigated, although lacking the 1,2-dithiol motif, is as effective as oltipraz at inducing detoxification enzymes and occurs through a transcriptional response. At what stage the transcriptional response coincides with the mechanism for other selective inducers of detoxifying enzymes is not known. It is unlikely to be coincident with the initial steps for oltipraz induction where the formation of mixed dithiols with proteins containing vicinal thiols has been implicated (Kensler et al., 1999). Whether it is the same final step as for phenolic antioxidant induction where Nrf2-MafK heterodimer interaction with gene regulatory elements is implicated (Itoh et al., 1997) is unknown. Regardless of the ultimate mechanism, 1,7-phenanthroline and perhaps other N-heterocycle-con-
taining compounds appear worthy of consideration as compounds with potential utility for chemoprotection.

Acknowledgments. We gratefully acknowledge the technical assistance of Nicole Bthers and Miriam Laker.

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