[Chem. Pharm. Bull.]
35(9)3838—3844(1987)

Studies on Poisonous Metals. XVIII.¹⁾ Effects of Several Dithiocarbamates on Tissue Distribution and Excretion of Cadmium in Rats

SHOJI KOJIMA,* MORIO KIYOZUMI, TOSHIYA HONDA, YOSHINOBU SENBA,
KAZUYOSHI KAMINAKA, and MIZUO OHNISHI

*Department of Hygienic Chemistry, Faculty of Pharmaceutical Sciences,
Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862, Japan*

(Received February 9, 1987)

The effects of various chelating agents, sodium *N*-benzyl-D-glucamine dithiocarbamate (NBGDTC), sodium *N*-*p*-methylbenzyl-D-glucamine dithiocarbamate (NMBGDTC), and sodium *N*-*p*-isopropylbenzyl-D-glucamine dithiocarbamate (NPBGDTC), which were newly synthesized, sodium *N*-methyl-D-glucamine dithiocarbamate (NMGDTC), diethyldithiocarbamate (DEDTC), dihydroxyethylthiocarbamate (DHEDTC), and dicarboxymethylthiocarbamate (DCMDTC), on the distribution and excretion of cadmium in rats were compared at 30 min and 24 h following cadmium injection. At 30 min after cadmium administration, these chelating agents all significantly enhanced the biliary excretion of cadmium, and at 24 h after cadmium injection, the chelating agents other than DEDTC and DCMDTC significantly enhanced the biliary excretion of the metal. The effects of NBGDTC, NMBGDTC, and NPBGDTC on the biliary excretion of cadmium were much larger than those of the other chelating agents. The urinary excretion of cadmium was increased by the chelating agents other than DEDTC and NPBGDTC. These chelating agents were effective in mobilizing cadmium from the liver, kidney, and pancreas at 30 min after treatment with cadmium. At both 30 min and 24 h after treatment with cadmium, NBGDTC, NMBGDTC, and NPBGDTC effectively depressed cadmium content in the liver without the mobilization of cadmium to the kidney. The chelating agents other than DEDTC did not result in the redistribution of cadmium to the brain, testes, lung, and heart. These results show that the injection of NBGDTC, NMBGDTC, or NPBGDTC at both 30 min and 24 h after treatment with cadmium can much more effectively mobilize cadmium from the body, mainly through the bile, without redistribution of cadmium to other tissues, such as brain, testes, lung, and heart, when compared with injection of other chelating agents. Furthermore, the pattern of mobilization and excretion of cadmium following treatment with each chelating agent was related to the organic/aqueous partition coefficient of each dithiocarbamate-cadmium complex.

Keywords—cadmium; tissue distribution; excretion; dithiocarbamate; chelate effect; partition coefficient

A single injection of cadmium into animals may result in a number of lesions in various organs, such as liver, testes, and sensory ganglia.²⁾ However, the kidney is the most sensitive organ to long-term exposure to cadmium, *i.e.*, the critical organ for this type of exposure.^{3,4)} Therefore, it is important to develop an effective chelator therapy for removal of cadmium to prevent cadmium-induced diseases. It has been reported that the biliary excretion of cadmium is an important excretory route after exposure to cadmium.⁵⁻⁸⁾ Since Sunderman achieved success in treating experimental and clinical nickel poisoning with diethyldithiocarbamate (DEDTC),⁹⁻¹²⁾ various dithiocarbamate compounds have been used in experimental cadmium poisoning in animals. DEDTC was more effective when treatment was delayed for some time than when it was given prior to or immediately after cadmium administration.^{13,14)} Some recent studies showed that injections of dithiocarbamates, such as dimethyldithiocarbamate,¹⁵⁾ DEDTC,¹⁵⁻¹⁸⁾ and diisopropyldithiocarbamate,¹⁵⁾ to mice pretreated with CdCl₂ 2 weeks

earlier, extensively reduced hepatic and renal cadmium burdens, but increased the cadmium load in the brain, testes, and heart. Repeated intraperitoneal injection of ammonium dihydroxydithiocarbamate (DHEDTC)¹⁷⁾ and sodium *N*-methyl-D-glucamine dithiocarbamate (NMGDTC)^{19,20)} into mice following exposure to cadmium resulted in substantial reduction in both the liver and kidney concentrations of cadmium without redistribution of cadmium to brain, testes, and heart. In addition, we reported that the injection of sodium *N*-benzyl-D-glucamine dithiocarbamate (NBGDTC), which was newly synthesized by us, into rats treated with cadmium was more effective in decreasing the cadmium concentration in the liver and kidney without the mobilization of cadmium to the kidney and without redistribution of cadmium to tissues such as the brain, testes, and heart, than injection of 2,3-dimercaptopropanol (BAL) or NMGDTC.^{21,22)}

In order to develop better chelating agents to mobilize cadmium from the body, we studied the comparative effects of NBGDTC, sodium *N*-*p*-methylbenzyl-D-glucamine dithiocarbamate (NMBGDTC), and sodium *N*-*p*-isopropylbenzyl-D-glucamine dithiocarbamate (NPBGDTC), which were newly synthesized by us, as well as NMGDTC, DEDTC, DHEDTC, and ammonium dicarboxymethyldithiocarbamate (DCMDTC), on the biliary and urinary excretion and tissue distribution of cadmium in rats at 30 min and 24 h after pretreatment with cadmium.

Experimental

Materials—¹⁰⁹Cd (specific activity, 1574 mCi/mg) was obtained from New England Nuclear (Boston, Mass.). Cadmium chloride and DEDTC were obtained from Wako Pure Chemical Ind. (Osaka). NMGDTC was prepared according to the procedure of Shinobu *et al.*¹⁹⁾ DHEDTC and DCMDTC were prepared by the reported methods.¹⁷⁾ NBGDTC was synthesized according to the procedure reported in our previous paper.²¹⁾ NMBGDTC and NPBGDTC were synthesized by the use of *N*-*p*-methylbenzyl-D-glucamine and *N*-*p*-isopropylbenzyl-D-glucamine,

Fig. 1. Structures of Dithiocarbamates Used

respectively, according to the method of our previous paper.²¹⁾ The products were analyzed, and the results were as follows. NMBGDTC. *Anal.* Calcd for $C_{15}H_{22}NNaO_5S_2 \cdot H_2O$: C, 44.87; H, 5.53; N, 3.49. Found: C, 44.35; H, 5.33; N, 3.60. NPBGDTC. *Anal.* Calcd for $C_{17}H_{26}NNaO_5S_2$: C, 49.61; H, 6.38; N, 3.40. Found: C, 49.12; H, 6.28; N, 3.31. Structural formulas of dithiocarbamates used are shown in Fig. 1. All other chemicals were of reagent grade.

Distribution and Excretion Studies—Male Wistar rats, weighing 190–230 g, were injected intraperitoneally with $^{109}CdCl_2$ (1 mg of Cd and $10 \mu Ci$ of $^{109}Cd/kg$) in 0.5 ml of physiological saline and housed in individual metabolic cages with drinking water and diet (Nosan Lab Chow) *ad libitum*. At 30 min or 24 h later, the rats were anesthetized with urethane (1 g/kg intraperitoneally) and the bile duct was cannulated with polyethylene tubing (PE 10) as described previously.⁸⁾ The rats were given intraperitoneally saline (control) or a chelating agent (400 $\mu mol/kg$) in 0.5 ml of saline. Bile and urine samples were collected for an experimental period of 3 h. Then, the rats were killed with urethane and various tissues were collected. The levels of ^{109}Cd radioactivity in the bile, urine and tissues were determined using an Aloka auto-well gamma scintillation counter (model ARC 300).

Determination of Partition Coefficients—The *n*-octanol/aqueous partition coefficient of each chelating agent–cadmium complex was determined according to the procedure in our previous paper²¹⁾ using 0.1 M Tris buffer (pH 7.4) as the aqueous solvent. The partition coefficients were expressed as $\log_{10}$ (cpm of ^{109}Cd in the *n*-octanol phase/cpm of ^{109}Cd in the aqueous phase).

Statistical Analysis—Data were compared by analysis of variance. When the analysis indicated a significant difference, the treated groups were compared to controls by means of Student's *t* test.

Results and Discussion

Table I shows the biliary and urinary excretions of cadmium when each chelating agent was injected 30 min after cadmium challenge. The results show that the major route of excretion of cadmium after injection of these chelating agents other than DCMDC into cadmium-exposed rats was *via* the bile. The biliary excretion of cadmium was significantly increased by injection of these chelating agents and was remarkably enhanced by treatment with DHEDTC, NMGDTC, NBGDTC, NMBGDTC, or NPBGDTC. In particular, benzyl- or alkylbenzyl-D-glucamine dithiocarbamates (NBGDTC, NMBGDTC, and NPBGDTC) showed an excellent enhancing effect on the biliary excretion of cadmium. In addition, DHEDTC, NMGDTC, and NBGDTC increased the urinary excretion of cadmium to a small extent, although DEDTC and NPBGDTC decreased the urinary excretion

TABLE I. Effects of Chelating Agents on Biliary and Urinary Excretions of Cadmium in Rats Pretreated with Cadmium, 30 min and 24 h Earlier

Chelating agent	Cadmium excreted/3 h (% of dose) ^{a)}			
	Cadmium pretreatment			
	30 min earlier		24 h earlier	
	Bile	Urine	Bile	Urine
Control	8.23 ± 0.61	0.005 ± 0.001	0.003 ± 0.002	0.005 ± 0.004
DEDTC	0.54 ± 0.11 ^{d)}	0.002 ± 0.001 ^{b)}	0.004 ± 0.002	0.031 ± 0.018
DHEDTC	24.60 ± 3.28 ^{b)}	0.23 ± 0.01 ^{d)}	0.21 ± 0.08 ^{b)}	0.034 ± 0.010 ^{d)}
DCMDC	2.52 ± 2.00 ^{d)}	3.96 ± 1.35 ^{e)}	0.003 ± 0.001	0.10 ± 0.05
NMGDTC	28.02 ± 0.58 ^{e)}	1.25 ± 0.12 ^{d)}	0.33 ± 0.11 ^{b)}	0.23 ± 0.05 ^{d)}
NBGDTC	46.36 ± 2.20 ^{e)}	0.34 ± 0.05 ^{c)}	10.32 ± 2.44 ^{d)}	0.23 ± 0.12 ^{b)}
NMBGDTC	42.91 ± 0.95 ^{e)}	0.082 ± 0.029	21.47 ± 2.38 ^{e)}	0.085 ± 0.040 ^{b)}
NPBGDTC	38.17 ± 2.48 ^{e)}	0.001 ± 0.001 ^{c)}	19.02 ± 2.00 ^{e)}	0.002 ± 0.001

The rats were injected with $^{109}CdCl_2$ (1 mg of Cd and $10 \mu Ci$ of $^{109}Cd/kg$). At 30 min or 24 h later they were injected intraperitoneally with saline or chelating agents (400 $\mu mol/kg$) and then bile and urine samples were collected for 3 h. a) The values represent the mean ± S.D. for 3 to 5 animals. Significantly different from the control values: b) $p < 0.05$; c) $p < 0.02$; d) $p < 0.01$; e) $p < 0.001$.

TABLE II. Effects of Chelating Agents on Tissue Distribution of Cadmium in Rats Pretreated with Cadmium 30 min Earlier

Chelating agent	Cadmium (% of dose) ^{a)}							
	Liver	Kidney	Pancreas	Heart	Testes	Lung	Spleen	Brain
Control	59.03 ± 3.54	2.05 ± 0.15	1.54 ± 0.09	0.30 ± 0.04	0.17 ± 0.02	0.23 ± 0.04	0.13 ± 0.02	0.031 ± 0.002
DEDTC	55.62 ± 2.15	1.64 ± 0.15 ^{c)}	0.96 ± 0.12 ^{d)}	0.29 ± 0.02	0.13 ± 0.01 ^{b)}	0.55 ± 0.09 ^{d)}	0.22 ± 0.04 ^{c)}	0.26 ± 0.02 ^{e)}
DHEDTC	41.07 ± 3.51 ^{d)}	2.28 ± 0.29	1.03 ± 0.23 ^{b)}	0.21 ± 0.03	0.15 ± 0.004	0.16 ± 0.04	0.085 ± 0.021	0.024 ± 0.005
DCMDTC	52.72 ± 2.44 ^{b)}	2.05 ± 0.16	1.10 ± 0.11 ^{d)}	0.26 ± 0.03	0.16 ± 0.01	0.19 ± 0.01	0.082 ± 0.010 ^{c)}	0.029 ± 0.002
NMGDTC	27.21 ± 1.19 ^{d)}	1.55 ± 0.15	1.08 ± 0.06 ^{d)}	0.24 ± 0.03	0.17 ± 0.02	0.14 ± 0.02 ^{b)}	0.11 ± 0.001	0.032 ± 0.005
NBGDTC	21.14 ± 3.42 ^{c)}	1.29 ± 0.12 ^{d)}	1.08 ± 0.11 ^{d)}	0.22 ± 0.02	0.14 ± 0.01	0.14 ± 0.01	0.10 ± 0.01	0.024 ± 0.004
NMBGDTC	21.07 ± 1.17 ^{c)}	1.37 ± 0.01 ^{b)}	0.95 ± 0.13 ^{d)}	0.21 ± 0.01 ^{b)}	0.14 ± 0.01	0.15 ± 0.01 ^{b)}	0.089 ± 0.008 ^{b)}	0.027 ± 0.002
NPBGDTC	18.65 ± 1.51 ^{d)}	1.41 ± 0.13 ^{c)}	1.07 ± 0.16 ^{b)}	0.23 ± 0.01	0.18 ± 0.01	0.21 ± 0.02	0.15 ± 0.04	0.022 ± 0.002

The rats were injected intraperitoneally with $^{109}\text{CdCl}_2$ (1 mg of Cd and 10 μCi of ^{109}Cd /kg). After 30 min, they were injected intraperitoneally with saline or chelating agents (400 μmol /kg). At the end of the experiment, the rats were killed and the tissue distribution of cadmium was determined from the radioactivity. ^{a)} Each value represents the mean $\pm$ S.D. for 3 to 5 animals. Significantly different from the control values: ^{b)} $p < 0.05$; ^{c)} $p < 0.02$; ^{d)} $p < 0.01$; ^{e)} $p < 0.001$.

TABLE III. Effects of Chelating Agents on Tissue Distribution of Cadmium in Rats Pretreated with Cadmium 24 h Earlier

Chelating agent	Cadmium (% of dose) ^{a)}							
	Liver	Kidney	Pancreas	Heart	Testes	Lung	Spleen	Brain
Control	52.99 ± 4.12	2.07 ± 0.40	3.09 ± 1.41	0.18 ± 0.04	0.20 ± 0.05	0.24 ± 0.05	0.21 ± 0.07	0.039 ± 0.008
DEDTC	52.14 ± 5.95	2.42 ± 0.24	1.71 ± 0.79	0.19 ± 0.01	0.19 ± 0.02	0.25 ± 0.04	0.21 ± 0.05	0.053 ± 0.004 ^{b)}
DHEDTC	57.08 ± 7.73	2.18 ± 0.03	1.18 ± 0.02	0.19 ± 0.04	0.21 ± 0.06	0.21 ± 0.03	0.32 ± 0.06	0.022 ± 0.003 ^{d)}
DCMDTC	59.06 ± 6.43	2.15 ± 0.05	1.35 ± 0.28	0.15 ± 0.004	0.18 ± 0.01	0.19 ± 0.02	0.23 ± 0.06	0.024 ± 0.001
NMGDTC	56.29 ± 4.23	2.46 ± 0.29	1.59 ± 0.56	0.17 ± 0.03	0.19 ± 0.04	0.17 ± 0.02	0.24 ± 0.04	0.040 ± 0.008
NBGDTC	42.70 ± 2.16 ^{b)}	1.93 ± 0.17	1.73 ± 0.69	0.19 ± 0.03	0.15 ± 0.01	0.15 ± 0.01	0.22 ± 0.04	0.027 ± 0.004
NMBGDTC	28.69 ± 1.72 ^{e)}	2.04 ± 0.09	2.03 ± 0.13	0.20 ± 0.03	0.19 ± 0.04	0.15 ± 0.03 ^{b)}	0.20 ± 0.05	0.030 ± 0.006
NPBGDTC	39.72 ± 4.48 ^{c)}	2.03 ± 0.10	1.66 ± 0.71	0.17 ± 0.01	0.20 ± 0.02	0.19 ± 0.01	0.31 ± 0.04	0.027 ± 0.005 ^{b)}

The rats were injected intraperitoneally with $^{109}\text{CdCl}_2$ (1 mg of Cd and 10 μCi of ^{109}Cd /kg). After 24 h, they were injected intraperitoneally with saline or chelating agents (400 μmol /kg). At the end of the experiment, the rats were killed and the tissue distribution of cadmium was determined from the radioactivity. ^{a)} Each value represents the mean $\pm$ S.D. for 3 to 5 animals. Significantly different from the control values: ^{b)} $p < 0.05$; ^{c)} $p < 0.02$; ^{d)} $p < 0.01$; ^{e)} $p < 0.001$.

of cadmium. DCMDTC among the chelating agents used showed the largest stimulatory effect on the urinary excretion of cadmium, and the major route of excretion of cadmium after injection of this chelating agent in cadmium-exposed rats was *via* the urine.

The tissue distribution of cadmium in rats treated with $^{109}\text{CdCl}_2$ and each chelating agent at the end of the experiment is shown in Table II. The percentages of cadmium deposited in the liver, kidney, and pancreas were significantly decreased by most of these chelating agents. The D-glucamine dithiocarbamate analogs (NMGDTC, NBGDTC, NMBGDTC, and NPBGDTC) remarkably reduced the cadmium content in the liver. DEDTC caused undesirable redistribution of cadmium to the tissues, such as brain, lung, and spleen. Gale *et al.*^{15,16)} reported that injections of dithiocarbamates, such as DEDTC and dimethyldithiocarbamate, into mice pretreated with cadmium caused the redistribution of cadmium to the brain, testes, and heart. However, NBGDTC, NMBGDTC, and NPBGDTC, which were synthesized by us, did not cause the redistribution of cadmium to brain, lung, testes, and heart.

The induction of metallothionein synthesis within a few hours after cadmium exposure has a marked effect on the pharmacokinetics and toxicity of cadmium.²³⁾ Thus, we examined the comparative effects of these chelating agents on the biliary and urinary excretions of cadmium when administered 24 h after pretreatment with cadmium, *i.e.*, after the synthesis of metallothionein (Table I). The excretion of cadmium in the bile, which is the major excretory

TABLE IV. Partition Coefficient of Cadmium Ion and Cadmium Complexes with Chelating Agents in *n*-Octanol/Aqueous System

Reaction mixture	Partition coefficient ^{a)} 0.1 M Tris buffer	Reaction mixture	Partition coefficient ^{a)} 0.1 M Tris buffer
Cd ion only	-3.13 ± 0.11	Cd+NMGDTC	-3.08 ± 0.02
Cd+DEDTC	3.77 ± 0.04	Cd+NBGDTC	0.30 ± 0.01
Cd+DHEDTC	-0.86 ± 0.01	Cd+NMBGDTC	1.35 ± 0.02
Cd+DCMDTC	-4.75 ± 0.17	Cd+NPBGDTC	3.16 ± 0.21

a) Expressed as $\log_{10}(\text{cpm in } n\text{-octanol phase/cpm in aqueous phase})$ at 37°C . Each value represents the mean $\pm$ S.D. for 3 individual measurements.

Fig. 2. Relationship between Biliary (A) or Urinary Excretion (B) of Cadmium and Partition Coefficient of Cadmium-Chelating Agent Complex

○, DEDTC; ●, DHEDTC; △, DCMDTC; ▲, NMGDTC; □, NBGDTC; ▽, NMBGDTC; ○, NPBGDTC. —, 30 min; ----, 24 h.

route of cadmium, was significantly increased by injection of DHEDTC, NMGDTC, NBGDTC, NMBGDTC, or NPBGDTC; NBGDTC, NMBGDTC, and NPBGDTC were the most effective. However, the delayed treatment with these chelating agents was less effective on the biliary excretion of cadmium than that at 30 min after cadmium exposure. The urinary excretion of cadmium was increased to a small extent by treatment with DHEDTC, NMGDTC, NBGDTC, and NMBGDTC, but was little affected by treatment with the other chelating agents.

Table III shows the tissue distribution of cadmium at 3 h after injection of the chelating agents into rats pretreated with cadmium 24 h earlier. Only NBGDTC, NMBGDTC, and NPBGDTC among these chelating agents significantly reduced the percentage of cadmium in the liver, the major site of accumulation of cadmium in the body, without the mobilization of cadmium to the kidney, and also tended to decrease the cadmium contents in the pancreas, lung, and brain. These results indicate that the injections of these 3 chelating agents can mobilize metallothionein-bound cadmium from the rat body even after the synthesis of metallothionein, leading to excretion of the metal mainly through the bile, as reported in our previous paper.^{1,21)} In addition, in the pretreatment with the chelating agents other than DEDTC, the undesirable redistribution of cadmium to the brain, testes, lung, and heart was not observed.

The partition coefficients of the complexes of cadmium with the chelating agents are listed in Table IV. In contrast to DEDTC, NPBGDTC, and NMBGDTC, which yield lipid-soluble complexes with cadmium, the complexes of cadmium with DCMDTC and NMGDTC had greater lipophobicity, and the complexes of cadmium with NBGDTC and DHEDTC yielded slightly positive and negative partition coefficient ($\log_{10}P$) values, respectively, indicating intermediate lipophobicity. Figure 2 shows the relationship between the biliary or urinary excretion of cadmium and the $\log_{10}P$ of the cadmium–chelating agent complex. In the treatment with the chelating agents at 30 min after cadmium exposure, the dithiocarbamates such as NMGDTC, DHEDTC, NBGDTC, NMBGDTC, and NPBGDTC, which form complexes with cadmium having $\log_{10}P$ values of about -3 to 3 , remarkably enhanced the biliary excretion of cadmium, resulting in decreased cadmium contents in the liver, kidney, and pancreas. On the other hand, in the treatment with the chelating agents at 24 h after cadmium exposure, NBGDTC, NMBGDTC, and NPBGDTC, which form complexes having $\log_{10}P$ values of about 0 to 3 , showed much larger stimulatory effects on the biliary excretion of cadmium, resulting in the decrease of cadmium content in the liver. In addition, NMGDTC and DCMDTC, which form complexes having $\log_{10}P$ values of about -3 to -5 , appeared to increase the urinary excretion of cadmium. DEDTC, which forms a complex having a $\log_{10}P$ value of about 4 , hardly increased the biliary or urinary excretion of cadmium, and caused the redistribution of cadmium to the brain. Jones and Jones²⁴⁾ have suggested that changes in the relative hydrophobic/hydrophilic character of the groups attached to the nitrogen atom of dithiocarbamates may be important in determining the antidotal activity of the compounds. The results of the present study also suggest that the pattern of distribution and excretion of cadmium after treatment with these chelating agents is related to the partition coefficients of the the cadmium–dithiocarbamate complexes and that NBGDTC, NMBGDTC, and NPBGDTC, in which the complexes with cadmium exhibit $\log_{10}P$ values of about 0 to 3 , are the most effective dithiocarbamates among the compounds examined in removing cadmium from the body (mainly about the bile) without the mobilization of cadmium to the kidney and without the redistribution of cadmium to other tissues, such as brain, testes, lung, and heart, at both 30 min and 24 h after treatment with cadmium.

References

- 1) Part XVII: S. Kojima, M. Kiyozumi, T. Honda, K. Kaminaka, Y. Oda, and Y. Senba, *Toxicology*, **45**, 93

- (1987).
- 2) L. Friberg, M. Piscator, G. F. Nordberg, and T. Kjellström, "Cadmium in the Environment," 2nd ed., CRC Press, Cleveland, 1974.
 - 3) M. Piscator, *Arch. Environ. Health*, **4**, 607 (1962).
 - 4) J. A. Bonnell, J. H. Ross, and E. King, *Br. J. Med.*, **17**, 69 (1960).
 - 5) F. Caujolle, J. Oustrin, and G. Silve-Mamy, *Eur. J. Toxicol.*, **4**, 310 (1974).
 - 6) M. Cikrt and M. Ticky, *Br. J. Ind. Med.*, **31**, 134 (1974).
 - 7) M. G. Cherian and J. J. Vostal, *Toxicol. Appl. Pharmacol.*, **29**, 141 (1974).
 - 8) S. Kojima, M. Kiyozumi, and K. Saito, *Chem. Pharm. Bull.*, **24**, 16 (1976).
 - 9) F. W. Sunderman, *J. New Drugs*, **4**, 154 (1964).
 - 10) F. W. Sunderman, *Ann. Clin. Res.*, **3**, 182 (1971).
 - 11) F. W. Sunderman, *Ann. Clin. Lab. Sci.*, **9**, 1 (1979).
 - 12) F. W. Sunderman, *Ann. Clin. Lab. Sci.*, **11**, 1 (1981).
 - 13) G. R. Gale, A. B. Smith, and E. M. Walker, Jr., *Ann. Clin. Lab. Sci.*, **11**, 476 (1981).
 - 14) S. G. Jones, M. A. Basinger, M. M. Jones, and S. J. Gibbs, *Res. Commun. Chem. Pathol. Pharmacol.*, **38**, 271 (1982).
 - 15) G. R. Gale, L. M. Atkins, E. M. Walker, Jr., A. B. Smith, and J. B. Hynes, *Ann. Clin. Lab. Sci.*, **13**, 207 (1983).
 - 16) G. R. Gale, L. M. Atkins, E. M. Walker, Jr., and A. B. Smith, *Ann. Clin. Lab. Sci.*, **13**, 425 (1983).
 - 17) G. R. Gale, L. M. Atkins, E. M. Walker, Jr., A. B. Smith, and M. M. Jones, *Ann. Clin. Lab. Sci.*, **13**, 474 (1983).
 - 18) G. R. Gale, E. M. Walker, Jr., and A. B. Smith, *Res. Commun. Chem. Pathol. Pharmacol.*, **41**, 293 (1983).
 - 19) L. A. Shinobu, S. G. Jones, and M. M. Jones, *Acta Pharmacol. Toxicol.*, **54**, 189 (1984).
 - 20) G. R. Gale, L. A. Shinobu, M. M. Jones, L. M. Atkins, and A. B. Smith, *Life Sci.*, **35**, 2571 (1984).
 - 21) S. Kojima, K. Kaminaka, M. Kiyozumi, and T. Honda, *Toxicol. Appl. Pharmacol.*, **83**, 516 (1986).
 - 22) S. Kojima, K. Kaminaka, M. Kiyozumi, and T. Honda, *Toxicol. Lett.*, **34**, 41 (1986).
 - 23) M. G. Cherian and R. A. Goyer, *Life Sci.*, **23**, 1 (1978).
 - 24) S. G. Jones and M. M. Jones, *Environ. Health Perspect.*, **54**, 285 (1984).