Arh hig rada toksikol 1989;40:165 – 181

Original Scientific Paper
UDC 612.357.4

BILIARY EXCRETION OF MERCURY AND CADMIUM*

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Received November 10, 1988

The own kinetic data on the biliary excretion of different mercury species and cadmium are presented. The role of enterohepatic circulation, mechanisms of biliary excretion and mobilization of Cd^{2+} and Hg^{2+} with selected chelating agents are discussed. The experimental results are confronted with scarce human data available from own laboratory and literature.

During the last two decades a great deal of information on the biliary excretion of xenobiotic, and important new data concerning biliary excretion of metals have been reported. From a broad spectrum of toxic metals those which are studied most often are mercury and cadmium. Almost all studies were performed in rats. Caution should be exercised when applying conclusions from animal experiments to man, especially when quantitative aspects of biliary excretion are concerned.

Although bile was first recognized as a route of excretion for some xenobiotics more than a hundred years ago, the main biochemical and physiological function traditionally attributed to bile was its role in fat digestion and elimination of a few compounds of physiological interest. The excretory function of bile is, however, much wider. More than two hundred compounds have been detected in bile, and an appreciable fraction of many chemicals appears in it.

A major reason why our knowledge of the biliary system had progressed so slowly was probably its relative inaccessibility. A problem in investigating hepatic excretion in

* Presented at the meeting held on the occasion of the 40th anniversary of the Institute for Medical Research and Occupational Health, University of Zagreb, Zagreb, November 9 – 10, 1988.

humans concerns bile sampling under physiological conditions. Surgery appreciably depresses bile flow and collection of bile with a cannula introduced into the duodenum is not currently provided. Studies with experimental animals are also very often confounded by the effects of anaesthesia and surgery, and some investigators have implanted chronic cannulae in the bile duct to measure biliary excretion in unrestrained animals. This technique has the disadvantages of continued loss of bile salts and other biliary constituents, and is therefore suitable only for acute short-term experiments. The techniques introduced recently, including a cannula that directs bile flow to the duodenum, promise to overcome these problems.

The literature provides data on the biliary excretion of a relatively great number of elements. It is very difficult to compare the experimental data in this field, because biliary excretion of elements has been studied under different experimental conditions: different routes of administration, doses, valency states, bile collection techniques, non-standard diets etc. Therefore, on the basis of the individual studies performed in various laboratories following different experimental protocols it is practically impossible to gain a comprehensive insight into the relative dispositional characteristics of different metals. It is always valuable to have the data from one

Table 1

Biliary and urinary excretion of metals in rats

Metal	Reference no.	Excretion/24 h (% of dose) Bile	Ratio (bile: urine)
^{52}Mn(II)chloride	(3)	28.8 ± 5.6	2215.3
^{110}Ag(I)nitrate	(20)	74.1 ± 4.0	185.2
Me^{203}Hg chloride	(7)	6.2 ± 0.7	29.524
^{64}Cu(II)chloride	(3)	31.06 ± 0.96	23.89
Ph^{203}Hg chloride	(7)	6.9 ± 0.8	9.2
^{210}Pb(II)nitrate	(3)	6.7	3.7
^{74}As(III)-Na_3AsO_3	(21)	10.82 ± 8.9	1.80
^{65}Zn(II)chloride	(21)	0.63 ± 0.38	1.235
^{203}Hg(II)chloride	(3)	3.8 ± 2.1	0.558
^{113}Sn(II)citrate	(23)	11.5 ± 2.4	0.49
^{115m}Cd(II)chloride	(24)	0.83 ± 0.18	0.488
^{51}Cr(VI)-Na_2CrO_4	(25)	3.51 ± 0.7	0.169
^{74}As(V)-Na_2HAsO_4	(21)	1.42 ± 0.75	0.048
^{58}Co(II)chloride	(26)	2.7 ± 2.0	0.037
^{51}Cr(III)chloride	(25)	0.51 ± 0.05	0.023
^{113}Sn(IV)citrate	(23)	0.1 ± 0.1	0.004

The elements in the table are arranged by their biliary:urinary excretion ratios. The values in the table are expressed in percentage of administered dose (mean values and their 95% confidence intervals or mean ± S.D.)
Me – methyl; Ph – phenyl

laboratory which were obtained from studies performed according to identical protocols and under similar experimental conditions. Such data can be directly compared.

The data in Table 1 show cumulative biliary excretion for several metals 24 hours after administration. The elements in the table are arranged by their biliary to urinary excretion ratios, starting with manganese with an impressively high ratio, and ending with Sn(IV), whose biliary excretion is practically zero. The results were obtained after the administration of a single dose.

The primary objective of the treatment of metal intoxication is to facilitate elimination of the toxicant from the organism. In order to do this on a rational basis, however, it is necessary to know the disposition of the metal, namely its distribution and excretion as well as the dose and time dependence of these processes (1).

Mercury and cadmium still have a high priority in toxicological research.

MERCURY

A fascinating aspect of the toxicology of mercury is the difference in the pattern of mercury deposition in organs and tissues following the administration of different mercury compounds. The dependence of organ distribution and clinical manifestations on the chemical form at entry is even more fascinating when one considers that, with the exception of short-chain alkylmercurials, all other forms of mercury are rapidly converted to sulphydryl-bound mercuric mercury. Even short-chain alkylmercurials – though at a greatly slower rate – are decomposed to mercuric mercury and before decomposition the intact methylmercury – like inorganic mercury – is mostly bound to sulphydryl binding sites.

Biliary excretion of mercurial compounds has been one of the most explored themes in recent years. Biliary excretion of inorganic and organomercurial compounds has been demonstrated directly in rats (2, 3). No direct data have been reported on the role of biliary excretion and reabsorption in humans, but the effectiveness of oral administration of polythiol resin in decreasing the body burden of mercury in methylmercury-poisoned patients has indirectly shown the biliary excretion of methylmercury (4).

Figure 1 shows curves of cumulative biliary excretion (Fig. 1A) and the rate of mercury excretion (Fig. 1B) in rats. The mercury elimination curve carries two typical peaks which require an explanation. The first peak corresponds, in our opinion, to an increased concentration of mercury in blood, occurring shortly after its intravenous administration. The second peak occurring 16 – 18 h after mercury administration is rather more difficult to explain. Our hypothesis is based on the assumption that mercury induces formation in the hepatocytes of specific protein carriers, which after combining with mercury are consequently excreted into the bile. Our attempts to inhibit induction by the administration of cycloheximide resulted in the disappearance of the second peak. On the other hand, mercury is known to bind easily with metallothionein. In order to reduce in the hepatocyte the concentration of mercury capable of inducing formation of specific carriers we induced metallothionein

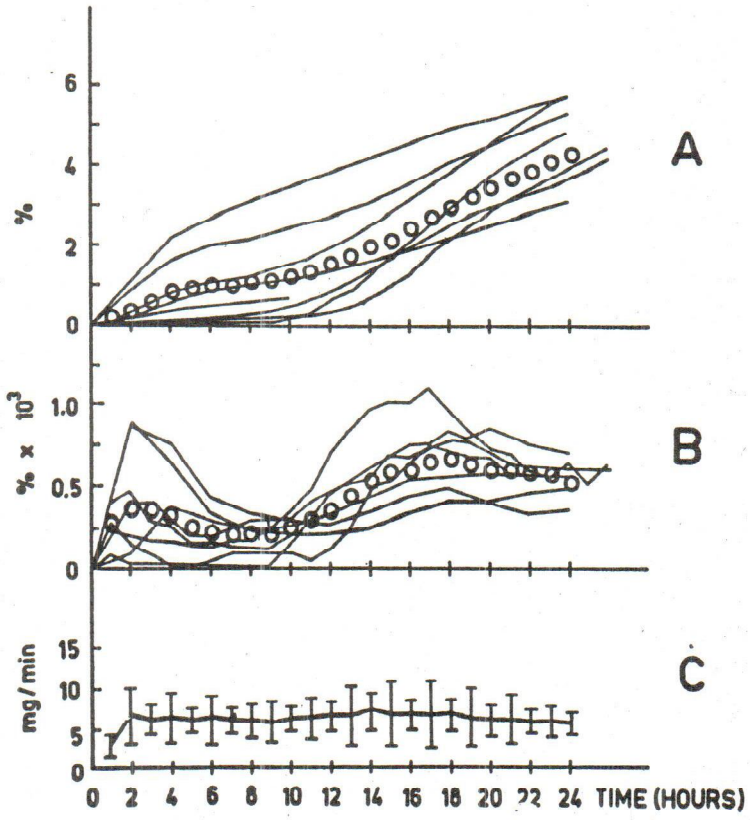

Figure 1. *Biliary excretion of 0.6 mg $^{203}Hg^{2+}$ per kg b.wt. administered intravenously over 24 hours; A – cumulative excretion as percentage of the administered dose; B – percentage of excreted ^{203}Hg per milligramme of bile; C – bile flow (mg/min) mean values and their 95% confidence intervals. Solid lines – results from individual rats; open circles – mean values.*

formation by previous administration of cadmium or zinc. In this case the biliary excretion of mercury in the second peak again became inhibited. These results seem to suggest that the formation of the specific protein carriers in the hepatocyte is induced about 8 – 12 h after mercury administration (5).

The biliary excretion of mercury after single injections of $HgCl_2$ or MeHgCl differs significantly. The rate of biliary excretion after a single i.v. injection of $HgCl_2$ is slower and the bile to plasma concentration ratio lower (6) than after an injection of MeHgCl (7).

We examined (8) the possibility of interactions between the doses of $HgCl_2$ or MeHgCl given in an interval of 48 hours and if the interaction exist whether it could affect the biliary excretion of mercury from either the first or second dose. Kinetic

studies indicate that each MeHg or Hg^0 dose is distributed independently from previous or subsequent doses. Our experiments indicate that this rule is valid for the biliary excretion of $Me^{203}Hg$. This apparent independent behaviour of doses does not apply to $HgCl_2$. Irrespectively of the differences in the biliary excretion of $HgCl_2$ and

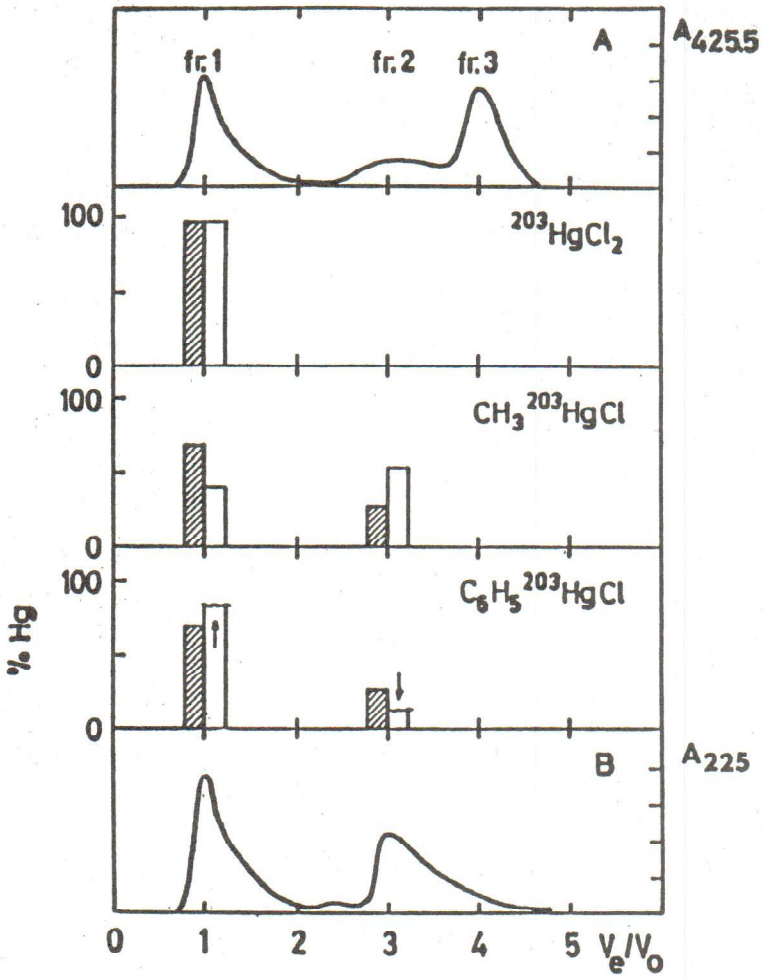

Figure 2. *Chromatographic fractionation on Sephadex G-100 of the bile collected in the first three hours and 24 hours after i.v. administration of different mercury compounds. Elution curves are plotted in absorbance values measured at 225 nm (lower part of diagram) and 425.5 nm (upper part). The middle part of diagram indicates distribution of radioactivity of ^{203}Hg between fraction I and II after administration of three mercury compounds (▨ 3 hours after administration, ▭ 24 hours after administration).*

MeHgCl a relatively low dose of $HgCl_2$ can depress biliary excretion of both $HgCl_2$ and MeHgCl. It is unlikely that the effect is connected with saturation of mercury transport.

The study of the mechanisms of metal biliary excretion is closely related to the problem of metal binding in the bile. Among the techniques most often used are the methods of electrophoretic and chromatographic bile fractionation. In this laboratory we used the method of disc electrophoresis and chromatographic fractionation of bile on a Sephadex G-100 column (9).

Figure 2 shows the results of the chromatographic fractionation of bile on a Sephadex G-100 column. The graph at the bottom of Figure 2 indicates the distribution of proteins on the chromatogram: there are two typical peaks – high molecular weight fraction 1 (m.w. higher than 150 000) and low molecular weight fraction 2 (m.w. about 10 000). The middle parts of the diagram show the distribution of ^{203}Hg between the bile fractions after intravenous administration of different mercury compounds to rats. Evidently, the distribution varies. In the upper part of the diagram there is the elution curve plotted in absorbance values measured at 425.5 nm (maximum absorbency of the yellow colour of bile). Three fractions are clearly visible: the first two are identical to high- and low-molecular weight fractions but there is also a third fraction, intensively yellow, which does not contain proteins (see the bottom diagram).

The binding of metal to the bile components may change during the time interval after metal administration. There is no doubt that differences in the binding of metal in the bile are also closely connected with the possible reabsorption of metal in the gastrointestinal tract in terms of its enterohepatic circulation. Generally speaking, the metal which is bound in the bile with bile components in fraction 2 (low molecular weight) is in this form readily reabsorbed in the intestine.

After intraduodenal administration of bile excreted mercury, the percent absorption of inorganic mercury was $21.1 \pm 10.7\%$ (10), and that of phenylmercury $17.7 - 25.6\%$ (7). *Norseth and Clarkson* reported (2) 9% absorption of inorganic mercury after 24 h, 40% of methylmercury after 2 h, and 70% after 6 h following administration. Similar rates of absorption of phenylmercury and inorganic mercury indirectly show the cleavage of C-Hg bond before biliary excretion.

In the future it will be necessary to devote much more attention to the possible mutual interaction of metals excreted via bile. The explanation of these interactions seems to be very diverse and at the moment one cannot formulate any convincing hypothesis.

The interaction between mercury and selenium can serve as an example. Selenite decreases methylmercury excretion in the rat bile probably by affecting its transfer from the protein mercaptide to glutathione (in liver cell) or by inhibiting methylmercury-glutathione complex formation (11). A simple complex binding between selenite and methylmercury does not explain the inhibition of biliary excretion of methylmercury.

In rats which were given an intravenous injection of $^{203}HgCl_2$ (0.6 mg of Hg^{2+} per kg b.wt.) we studied the effect of intraperitoneal administration of selenite or selenate (0.525 mg of Se per kg b.wt.) on the biliary excretion of ^{203}Hg. Both selenium species injected immediately after mercury significantly decreased urinary as well as biliary

excretion of ^{203}Hg. A transient increase of the rate of biliary excretion of ^{203}Hg during the first two hours after administration was observed in rats treated with selenate

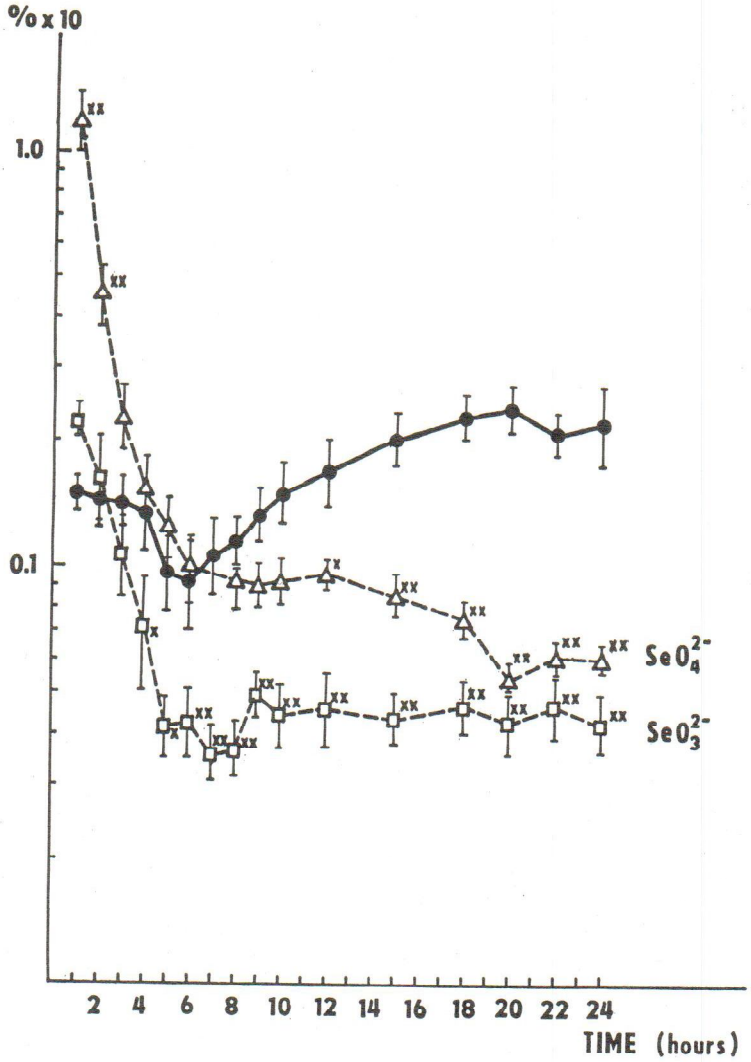

Figure 3. *Rate of biliary excretion of ^{203}Hg during 24 hours after administration of $^{203}HgCl_2$ (0.6 mg of Hg^{2+} per kg b.wt.). The effect of selenite (●——●) or selenate (△– –△) administration. Control animals (□– – –□). Selenite and selenate were administered at the same dose 0.525 mg of Se per kg b.wt. i.p. immediately after ^{203}Hg injection.*
*The results are expressed as percentages of the administered dose of ^{203}Hg per mg of bile ($\times 10^3$) (means and 95% confidence intervals for means). Statistically significant difference in comparison with control group: * ($p < 0.005$), ** ($p < 0.01$).*

(Figure 3). This finding seems to support the idea that the reduction of selenate to selenite which is a crucial step in biotransformation of selenium in the body is not instant but takes some time.

A better understanding of the biliary excretion of toxic metals might consequently result in the development of effective therapeutic methods based on the enhanced elimination of metals from the organism.

In our laboratory a variety of compounds were tested of which spironolactone (SPL), Unithiol (UNI) (sodium 2,3-dimercapto-1-propanesulphonate), thiomestrone and BAL were the most effective ones in the mobilization of mercury via bile (12). We studied the combined effect of UNI and SPL on distribution and excretion of mercury in rats. Administration of UNI increased significantly biliary excretion of mercury (Figure 4).

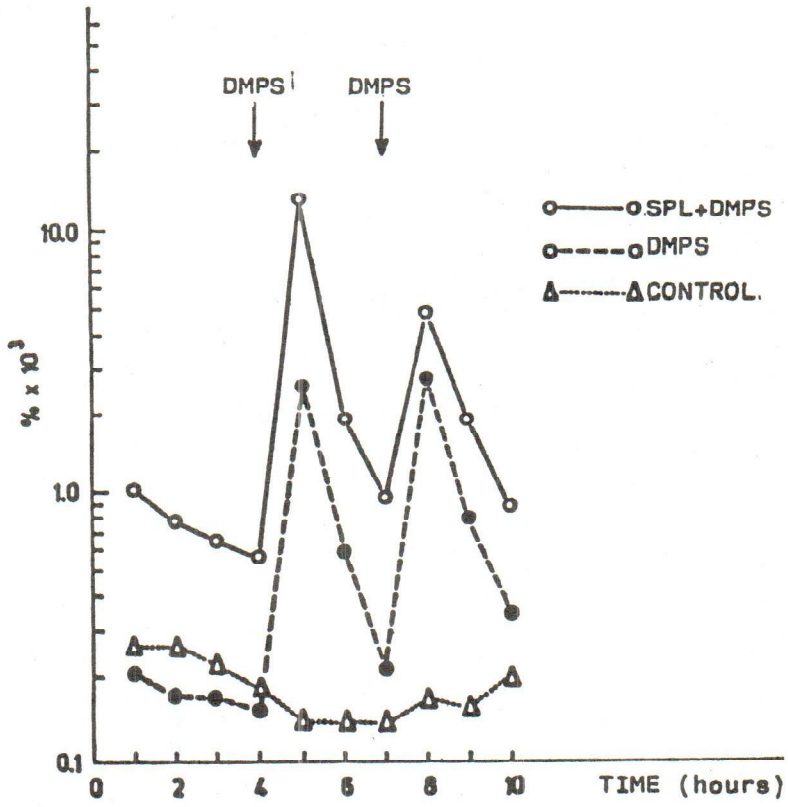

Figure 4. *Biliary excretion of ^{203}Hg during 10 hours after administration of $^{203}HgCl_2$ (120 μg of Hg^{2+}/rat, i.v.). The influence of unitiol (UNI) and spironolactone (SPL) treatment. The values are expressed as percentages of the administered dose of ^{203}Hg excreted per milligramme of bile. Arrows indicate UNI administration (dose: 12.5 mg of UNI per rat-i.m.). SPL pretreatment: SPL was administered by gavage into stomach 24, 16 and 2 h before mercury injection (dose: 10 mg of SPL per rat).*

The effect of UNI is, however, time limited, probably because of its rapid elimination from the body. After SPL pretreatment the effect of UNI on the biliary excretion of mercury was significantly higher. We did not find any differences between UNI and UNI+SPL groups of animals in the total amount of mercury excreted from the body during 24 h after administration, but we detected lower levels of ^{203}Hg in the kidney and brain in the UNI+SPL treated group (Table 2) (13).

Table 2

^{203}Hg excretion in rats 24 hours after i.v. administration of $^{203}HgCl_2$

Group	n	Urine	Faeces + + content of GIT	Total excretion
DMPS	4	32.8±0.6	11.0±0.9	43.8
SPL	4	3.9±1.3	27.9±4.9	31.7
DMPS + SPL	4	17.2±2.7	29.6±2.3	46.8
Controls	4	7.4±0.4	7.2±0.6	14.6

DMPS – Unithiol treatment (12.5 mg of DMPS per rat i.m. 4 and 7 h after administration of ^{203}Hg)
SPL – Spironolactone pretreatment (10 mg of SPL per rat by gavage into stomach 24, 16 and 2 h before ^{203}Hg injection)
DMPS+SPL – Unitihiol and Spironolactone treatment (the same dose and the same time intervals as described above)
^{203}Hg was administered intravenously in the form of $^{203}HgCl_2$ (120 μg of Hg^{2+} per rat). Values in the Table are expressed as percentages of the administered dose of ^{203}Hg (mean values and their 95% confidence intervals). For plasma the results are expressed in terms of the entire plasma volume (8.3 ml per 200 g rat).
GTT – gastrointestinal tract

In rats which were administered $^{203}HgCl_2$ intravenously we tested the effect of the combined treatment with polythiol resin, SPL, and UNI on the whole body retention, distribution and excretion of ^{203}Hg within 48 h after administration (14). In comparison with a group of rats treated with UNI alone, no significant differences were detected in the whole body retention and excretion of ^{203}Hg in rats treated with the combination of agents. A significant decrease, however, in the content of ^{203}Hg in the kidney, plasma and brain suggests that the combination is therapeutically more effective.

In workers exposed to metallic mercury (manufacture of thermometers and electrolytic production of chlorine) for several years (5–31 years), the effects of UNI and UNI+SPL on the urinary and biliary excretion of mercury were tested. The administration of UNI (5 ml of a 5% solution i.m.) significantly increased (up to 200-fold) the mercury concentration in the urine of the exposed group (Figure 5). Also, in the control persons, the administration of UNI significantly increased the mercury concentration in the urine as compared with the original values (20-fold on the average). Figure 6 shows the biliary excretion of mercury in control persons and in exposed workers after administration of SPL, UNI and UNI+SPL. After the combined treatment the concentration of mercury in the bile was the highest (15).

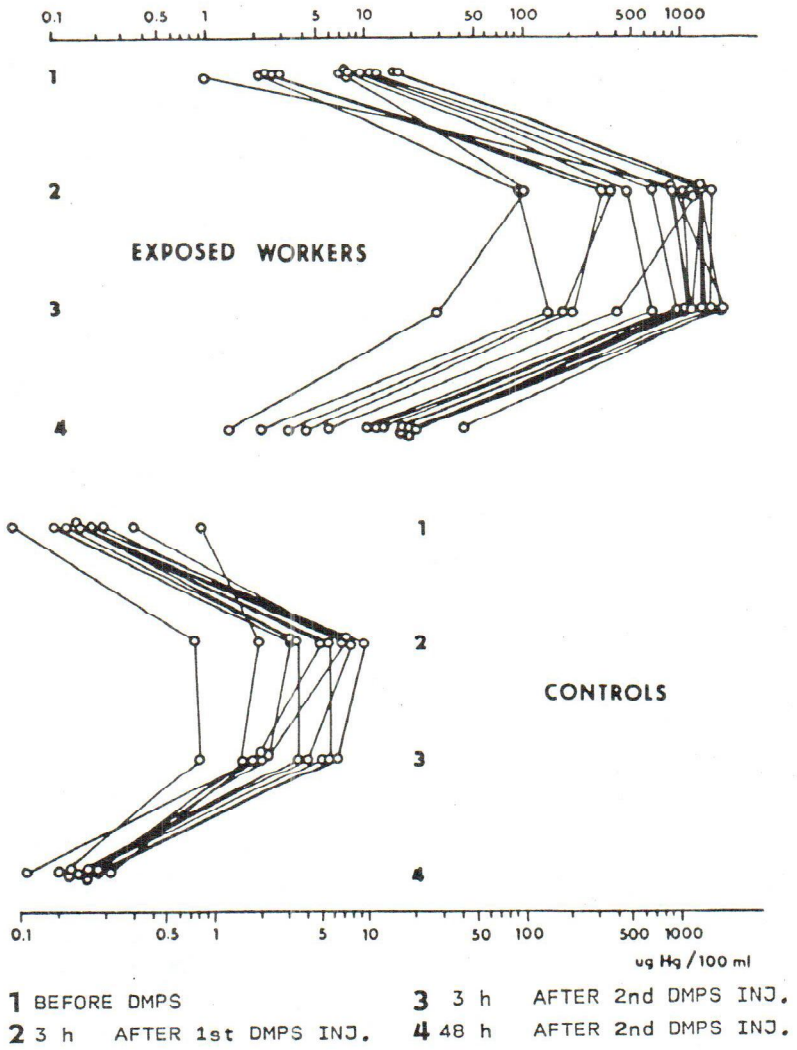

Figure 5. *Mercury concentration in the urine of exposed and control workers. The effect of two i.m. injections of 5 ml 5% Unithiol.*

CADMIUM

Cadmium in mammalian body induces the synthesis of metallothionein which bonds cadmium very firmly in the liver, kidneys, and other organs. Mammalian species

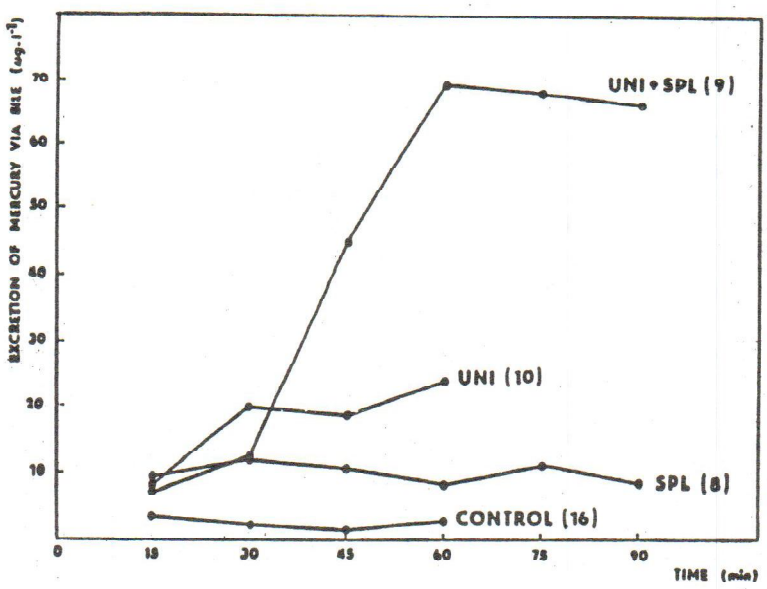

Figure 6. *Mercury concentration in the bile of exposed and control workers during 90 min after $MgSO_4$ p.o. administration. The effects of UNI, SPL and UNI+ SPL. UNI: 5 ml 5% i.m., SPL: 8 doses of SPL (25 mg each) administered p.o. during 60 hours before bile collection.*

Table 3

Biliary excretion of cadmium in rats: dose and cadmium pretreatment

Dose (μg of Cd/kg)	Biliary excretion/5 h (% of dose)	Reference no.
100	0.065 ± 0.02	(16)
250	0.33	(29)
335	0.45 ± 0.17	(24)
450	0.45 ± 0.18	(24)
500	1.60 ± 0.03	(16)
600	4.80 ± 1.74	(24)
750	3.6 ± 0.16	(16)
1000	5.6 ± 0.45	(16)
1250	5.62 ± 0.92[a]	(27)
1500	10.4 ± 0.32	(16)
1500 – 2500	15.7 ± 1.49[a]	(28)
2000	16.9 ± 1.2	(16)
2625	20.06 ± 2.55[a]	(27)
1250 PRE	0.03 ± 0.02[a]	(27)
2625 PRE	0.07 ± 0.01[a]	(27)

PRE – The rats were pretreated with 2 s.c. doses of $CdCl_2$ (2.5 mg of Cd/kg body wt.) at 48-h intervals. After further 5 days the rats were given a single i.v. injection of $CdCl_2$ in the doses of 1.25 or 2.625 mg of Cd/kg body wt.
[a]Biliary excretion of Cd/4 h

excrete cadmium very slowly – the biological half-time in man is between 10 and 30 years for the liver and kidneys.

Biliary excretion of cadmium within 24 hours after administration is very low. The highest rate is reached between 15 and 30 minutes after dosing. Table 3 shows data on biliary excretion of cadmium in dependence on the dose (5). With increasing dose the percentage of cadmium excreted via bile increases. Here we can also observe the effect of repeated cadmium administration on its biliary excretion. The two last lines of Table 3 refer to biliary excretion of ^{115m}Cd after cadmium pretreatment. When we compare these data with those measured without pretreatment it is quite evident that the pretreatment causes a significant decrease in the cumulative biliary excretion of this element. Cadmium pretreatment induces formation of metallothionein in the liver, resulting in an increased cadmium retention, since the cadmium-metallothionein complex is only poorly excreted in the bile.

Table 4 shows the amounts of cadmium found in both bile fractions (I and II) after chromatographic fractination in relation to the dose administered and pretreatment

Table 4

The effects of dose and cadmium pretreatment on the binding of cadmium in rat bile (27)

Dose (mg of Cd/kg b wt)	Fraction I	Fraction II	Cumulative biliary excretion per 5 h (% of dose)
0.6	55.8 (43.0 – 68.6)	44.2 (31.4 – 57.0)	4.8 ± 1.7
0.6 PRE-B	85.3 (82.5 – 88.2)	14.7 (11.8 – 17.5)	0.03 ± 0.01
1.25	9.3 (8.1 – 10.2)	90.7 (88.1 – 92.6)	5.6 ± 0.9
1.25 PRE-A	83.5 (80.6 – 86.4)	16.5 (13.6 – 19.4)	0.03 ± 0.02
2.625	3.1	96.9	12.1 ± 2.5
2.625 PRE-A	87.2 (84.4 – 90.0)	12.8 (10.0 – 15.6)	0.07 ± 0.01

The bile, collected 0 – 3 after i.v. administration of $CdCl_2$, was fractionated using column chromatography (Sephadex G-100). Fraction I (V_e/V_0) at »void volume«. Fraction II (V_e/V_0 at 2.8 – 3.4). The conditions of the chromatographic separation are given in the legend to the figure.
PRE-A – The rats were pretreated with 2 s.c. doses of $CdCl_2$ (2.5 mg of Cd/kg b.wt.) at 48-h-intervals. After 5 further days the rats were given a single i.v. injection of $CdCl_2$ in the doses of 1.25 or 2.625 mg of Cd/kg b.wt.
PRE-B – The rats were pretreated with single i.v. doses of $CdCl_2$ (0.6 mg of Cd/kg b.wt.). After 20 h have elapsed, the 2nd i.v. dose of $CdCl_2$ (0.6 mg of Cd/kg b.wt.) was administered. The values shown in table are expressed as percentages of the total quantity of Cd found in both fractions I and II (means and limit values from 1 – 3 chromatographic fractionations). In the case of cumulative biliary excretion of cadmium – means and 95% confidence intervals for means; number of rats: 6 – 8.

with cadmium. Table 4 clearly shows that the cadmium content of the low-molecular weight fraction II increases when higher cadmium doses are administered. On the contrary, pretreatment with cadmium increases cadmium content in the high-molecular weight fraction I. These results are in good conformity with cumulative biliary excretion of cadmium. With increasing dose of cadmium, its cumulative biliary excretion increases. It may be therefore said that cumulative biliary excretion of cadmium correlates with its content in the low-molecular weight fraction II. In the case of pretreatment cadmium content in fraction II decreases, and similarly, there is a decrease in its biliary excretion. After i.v. injection of 2 mg of Cd/kg b.wt. more than 98% of the cadmium in bile samples was associated with a low-molecular weight compound, with molecular weight less than 4000 (probably Cd-glutathione complex). After administration of 2.625 mg Cd/kg b.wt. 96.6% of cadmium was retained in fraction II (Table 4). According to *Cherian and Vostal* (16), the low cumulative biliary excretion of cadmium and the higher percentage of its accumulation in the liver in rats given low doses suggest that the liver, initially, has a high affinity for cadmium and therefore only a small percentage of it is transported to the bile. With higher cadmium doses the binding sites in the liver may be saturated and more cadmium becomes available for biliary excretion. In that case cadmium might form a complex with low-molecular weight compounds in the bile. Therefore there seems to exist a correlation between the liver binding capacity for cadmium, its cumulative biliary excretion and the binding of cadmium in the bile.

We tested the effects of several dithiocarbamate analogues on biliary and urinary excretion and organ distribution of cadmium in rats drinking cadmium-containing water. In the first experiment the effect of sodium diethanolamine dithiocarbamate (DEDTC) was studied in three different groups of rats drinking water with three different cadmium concentrations (5, 10 and 50 mg/L) for a period of three months (17). DEDTC administration (500 mg/kg, i.p.) in all exposed groups significantly increased biliary excretion of cadmium (Figure 7). With the exception of animals which received water containing the lowest cadmium concentration (5 mg/L) the urinary excretion also increased. In rats exposed to the highest cadmium concentration cadmium content in the liver and kidney after DEDTC injection significantly decreased. To exclude the possibility that DEDTC preferentially mobilized cadmium atoms, which had been newly deposited in the body according to the »last-in-first-out« principle (18), we studied the effect of DEDTC on cadmium excretion one month after termination of a three-month exposure to 50 mg/L of cadmium in drinking water. Moreover, we studied the effects of other dithiocarbamates: N-methyl-D-glucamine dithiocarbamate (MGDTC) and isonipecotamide dithiocarbamate (INADTC). All dithiocarbamates tested were administered at equimolar doses of 2.46 mmol/kg. Biliary excretion of cadmium significantly stronger not only after the first but also after the second injection of dithiocarbamates (Figure 8); in the case of DEDTC the effect of the second injection was significantly stronger than that of the first injection. During 12 hours after administration of the first injection of DEDTC 15.9 μg of cadmium was excreted via urine and 124.4 μg via bile. After administration of MGDTC cadmium excretion was 14.5 and 47 μg, while in the case of INADTC it was 23.6 and 7.9 μg

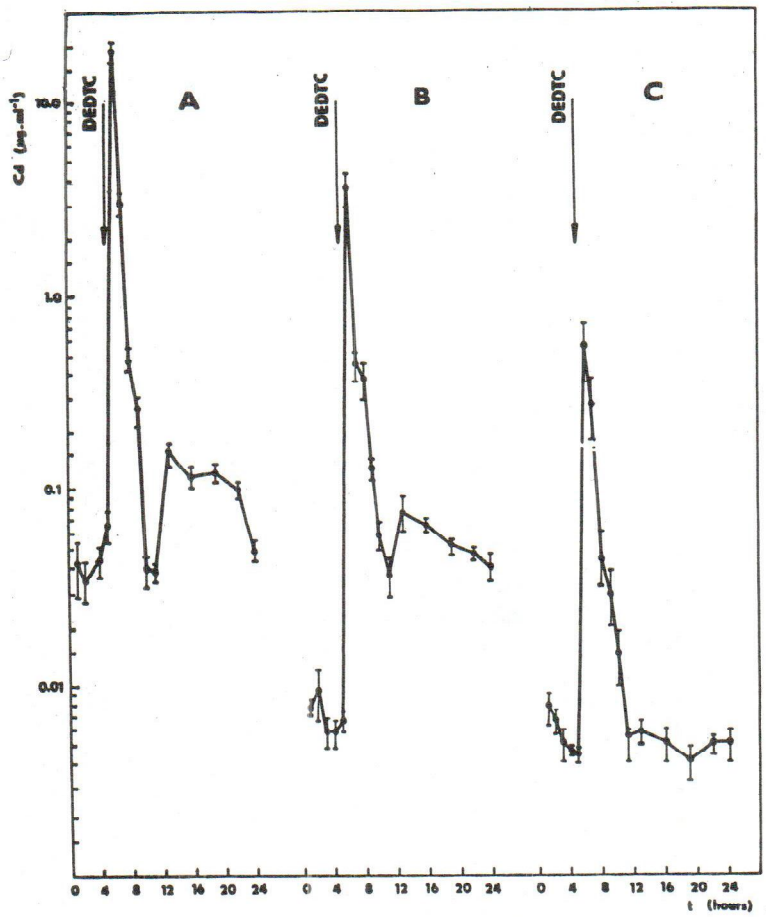

Figure 7. *Biliary excretion of cadmium. The effect of DEDTC administration. Cd concentration in drinking water: group A 50 mg/L, group B 10 mg/L, group C 5 mg/L. DEDTC was administered i.p. at the dose of 500 mg/kg.*

respectively. In control animals urinary and biliary excretion per 12 hours reached only 0.09 and 0.12 μg Cd. With all the chelates tested cadmium concentrations in the liver and kidney were significantly decreased. Unfortunately, after DEDTC administration cadmium level in the brain tissue increased (19).

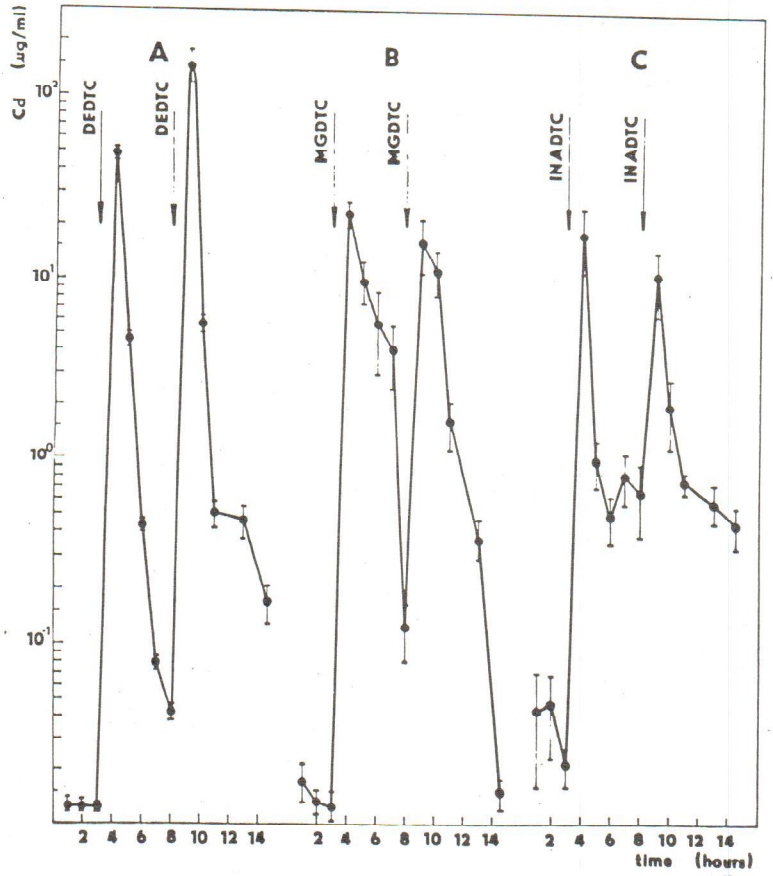

Figure 8. *Biliary excretion of Cd in rats one month after termination of a three-month exposure to Cd in drinking water (50 mg/L). The effects of DEDTC, MGDTC, and INADTC administered i.p. two times at the equimolar doses of 2.46 mmol/kg. Arrows indicate the time of administration.*

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Sažetak

IZLUČIVANJE ŽIVE I KADMIJA PUTEM ŽUČI

U radu su izneseni vlastiti rezultati istraživanja izlučivanja žive i kadmija putem žuči. Raspravlja se o enterohepatičkoj cirkulaciji, mehanizmu izlučivanja putem žuči, kao i o mobilizaciji Cd^{2+} i Hg^{2+} pomoću odgovarajućih kelirajućih supstancija. Dobiveni rezultati uspoređeni su s rijetkim podacima dobivenim na ljudima koji su bili dostupni u našem laboratoriju i u literaturi.

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