

# Influence of Age on Metal Metabolism and Toxicity

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The metabolism and toxicity of lead, cadmium, mercury, and manganese in the postnatal period was studied in rats. Absorption, whole body retention, and organ distribution of  $^{203}\text{Pb}$ ,  $^{115\text{m}}\text{Cd}$ ,  $^{203}\text{Hg}$ , and  $^{54}\text{Mn}$  were determined after oral and parenteral administration of these radioisotopes. The acute oral toxicity ( $\text{LD}_{50}$ ) was determined after a single application of metal chlorides. The results obtained in sucklings show a very high intestinal absorption of all metals which is partly attributed to milk diet; a higher whole body retention, higher blood levels and a much higher accumulation in the brain; and a higher oral toxicity.

These results indicate age specific differences in the pharmacokinetics of metals in sucklings. It seems reasonable to consider the early neonatal age as a critical period for metal accumulation and therefore for metal toxicity.

The results are interpreted on the basis of current concepts of developmental physiology and pharmacology and suggestions for future research trends are made.

All environmental chemicals which enter into the biological cycle have the potential of entering into the human body at all stages of its development. Metals represent a group of special concern, since the concentration of some toxic metals in the environment has already reached levels which might be harmful especially if combined with other factors which increase the metals' absorption, retention and toxicity. The question is raised whether the young, from birth and onward, might be more sensitive to toxic metals in the environment than are adults. A conclusive answer is difficult to give since for ethical reasons most of the data available at present have been obtained on animals. Moreover, many stages in the mammalian development cycle can be considered as "critical" in themselves, so that to assess the possible effects of an exposure in terms of the chemical form, dose, or route of administration of a metal is extremely difficult. A new field of developmental toxicology will have to be established in order to elucidate critical biochemical processes in the immature organism that might be responsible for differences in the metabolism and

toxicity of metals in these members of the population as compared to adults.

The transfer of metals from mother to embryo and fetus and the gametotoxic, embryotoxic and fetotoxic properties of lead, cadmium, and mercury have been adequately reviewed in publications from earlier meetings of the Scientific Committee on the Toxicology of Metals (1-3). It is, however, astonishing how little information is available on the pharmacokinetics and effects of metals during the immediate postnatal period. This period, in which rapid changes in organ function and development occur and in which milk is the only nutritional source, has been neglected from the standpoints of both pharmacology (4) and environmental toxicology. The realization that exposure to toxic metals during the early neonatal period might cause irreversible behavioral (5, 6) and other changes seems at least to be receiving proper research efforts.

We shall present here some of our previously published data (7-10) and our new results on the absorption, retention, distribution, and toxicity of inorganic lead, cadmium, mercury, and manganese in suckling rats. All experiments were performed in the same laboratory with a similar technique and therefore the results which they yielded are considered to be conclusive in several respects. Namely,

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early postnatal age represents a period during which a higher absorption and retention and therefore a higher toxicity can be expected. These results are also in general agreement with some data from other laboratories, which have recently been reviewed (11).

## Material and Methods

All experiments were performed on albino rats of different ages. During the experiment, suckling rats aged one and two weeks were kept in a litter of six together with their mothers. Weanling rats and older rats were fed a stock laboratory diet (1.2% Ca and 0.8% P). Cow's milk was used in experiments in which rats received a "milk diet" ad libitum.

In pharmacokinetic studies of metal absorption and distribution radioactive isotopes of lead ( $^{203}\text{Pb}$ ) cadmium ( $^{115\text{m}}\text{Cd}$ ), mercury ( $^{203}\text{Hg}$ ), and manganese ( $^{54}\text{Mn}$ ) were given either orally, by the method of gastric intubation or by the method of artificial feeding described by Kostial et al. (12), or parenterally by intravenous or intraperitoneal injection. The radioactive isotopes of cadmium, mercury, and manganese were supplied by the Radiochemical Center, Amersham, England and those of lead by the Gustaf Werner Institute, Uppsala, Sweden. All isotopes were administered as chlorides of a high specific activity except for  $^{115\text{m}}\text{Cd}$ , which contained 0.5–1 mCi/mg Cd.

The retention in the whole body and in the liver, both kidneys, brain, and blood was determined by scintillation counting six days after administration of the radioisotopes. Blood values were recalculated on basis of total blood by use of theoretical blood volumes for rats according to Belcher and Harriss (13). The results are expressed as the percentage of the dose administered and presented as the arithmetic mean and standard error of the mean for each group of animals.

The toxicity of cadmium, mercury, and manganese chloride was determined in animals of five different age groups (2, 3, 6, 20, and 54 weeks). Metal chlorides were administered by stomach tube in a volume of 1 ml/200 g of body weight. Six dose levels were used in each age group. Each dose level was tested on six animals. The  $\text{LD}_{50}$  values and the 95% confidence limits were calculated by the method of moving averages (14) 8 days after a single oral administration.

## Results and Discussion

### Gastrointestinal Absorption

The results which we obtained in suckling rats show a very high absorption of lead, mercury, cad-

mium, and manganese ranging from 26 to 52% of the oral dose as compared to absorption values of below 1% in older rats on a standard rat diet (Table 1). These results are in agreement with our previously published data on lead absorption in suckling rats (12, 15).

A higher absorption of lead in the young was confirmed by Forbes and Reina (16) in rats and by Alexander et al. (17, 18) in infants. A higher absorption of several other cations in young animals has been noted by some other authors indicating that increased absorption at this age might be a general phenomenon, e.g., plutonium (19), zirconium, niobium, cerium (20), radium (21), cerium (22), palladium (23), manganese (24), etc. The high absorption, which in most experiments lasted only until weaning, was mainly attributed to pinocytotic activity, which is generally very pronounced in the very young (25, 26).

We assumed that the milk diet could be an important factor in the increased metal absorption in the sucklings since we also found a very high absorption of lead in older animals fed a milk diet (9). The results in Table 1 confirm this assumption. Older rats on a milk diet also showed a higher absorption of cadmium, mercury and manganese, although values were never as high as in suckling rats. Some other authors have also observed that milk causes increased absorption of some heavy metals, e.g., radium (21), cerium (22), plutonium (19). Changes in the diet might thus be a major factor in the sudden decrease in metal absorption in the young. The mechanism by which milk enhances metal absorption is still uncertain. We assumed that the effect was not due to differences in the calcium, phosphate, or vitamin D content because in our experiments rats on a control diet had similar daily intakes of these elements as had the animals on the milk diet (9). The effect is likely to be due to metal binding to some milk constituents which might be more available for absorption (9) and also to essential trace element deficiency in milk. This certainly applies to iron, which is known to be low in milk and is also known to influence the absorption and toxicity of metals (5, 27, 28). There is no doubt that our results on manganese absorption were influenced by the lower manganese content in the milk (24). However, in some of our experiments, rats which received milk with manganese additives still showed higher absorption than animals on a control diet with the same manganese level (29).

### Retention and Distribution

When radioactive isotopes were given by parenteral injection to avoid differences in intestinal absorption due to age, other differences in the me-

**Table 1. Influence of age and milk diet on lead, cadmium, mercury, and manganese absorption in rats.<sup>a</sup>**

Radio-isotope	Absorption, % of oral dose <sup>b</sup>					
	Age, weeks (n)	Sucklings	Older animals			
			Age, weeks (n)	Milk diet	Age, weeks (n)	Standard diet
<sup>203</sup> Pb	1 (18)	52.05 ± 1.65	6 (24)	22.9 ± 2.15 <sup>c</sup>	6 (20)	0.40 ± 0.09 <sup>c</sup>
<sup>115m</sup> Cd	1 (24)	25.61 ± 2.0	6 (10)	6.86 ± 0.24	6 (10)	0.49 ± 0.02
<sup>203</sup> Hg	1 (23)	38.21 ± 1.50	18 (11)	6.73 ± 0.83	18 (11)	0.99 ± 0.05
<sup>54</sup> Mn	1 (18)	39.9 ± 1.5	6 (15)	6.4 ± 0.4	6 (11)	0.05 ± 0.004

<sup>a</sup> Sucklings received radioactive isotopes in cow's milk enriched with CaCl<sub>2</sub> and KH<sub>2</sub>PO<sub>4</sub> to the level of rat's milk in the total volume of 0.5 ml using the artificial feeding method described by Kostial, Simonović, and Pišonić (12).

<sup>b</sup> Percentage oral dose in whole body 6 days after administration. Values are presented as arithmetic mean ± SE; number of animals in parentheses.

<sup>c</sup> Data from Kello and Kostial (9).

**Table 2. Retention and distribution of lead, mercury, cadmium and manganese in rats in relation to age.<sup>a</sup>**

Subjects	Radio-isotope	Age, weeks	Admin. route	Distribution, % dose				
				Whole body	Whole blood	Liver	Kidneys	Brain
Sucklings (males and females)	<sup>203</sup> Pb	2 (12)	IP	88.6	1.52	1.23	0.93	0.243 <sup>b</sup>
				0.9	0.07	0.06	0.04	0.009
	<sup>203</sup> Hg	2 (6)	IV	77.8	0.53	9.23	27.72	0.52 <sup>c</sup>
				0.6	0.03	0.42	0.29	0.02
	<sup>115m</sup> Cd	1 (22)	IP	88.6	1.25	46.11	6.08	<sup>d</sup>
<sup>54</sup> Mn	1 (7)	IP	1.0	0.02	0.75	0.16	—	
			93.1	0.253	8.7	1.9	7.2	
Older rats (females)	<sup>203</sup> Pb	17 (6)	IP	2.8	0.013	0.5	0.1	0.4
				38.7	0.72	1.38	2.74	0.031 <sup>b</sup>
	<sup>203</sup> Hg	21 (6)	IV	1.3	0.06	0.14	0.14	0.003
				56.1	0.21	0.70	51.21	0.027 <sup>c</sup>
	<sup>115m</sup> Cd	6 (9)	IP	1.3	0.01	0.03	0.77	0.001
				77.9	0.48	55.65	4.77	<sup>d</sup>
	<sup>54</sup> Mn	6 (10)	IP	0.9	0.02	0.78	0.12	—
				28.9	0.044	4.8	1.3	0.26
				0.4	0.002	0.3	0.05	0.02

<sup>a</sup> Values obtained 6 days after radioisotope administration. With <sup>115m</sup>Cd values were obtained 14 days after application. Values presented as arithmetic mean and SE. Age of animals given at the time of radioisotope administration; number of animals in brackets.

<sup>b</sup> Data from Momčilović and Kostial (7).

<sup>c</sup> Data from Jugo (8).

<sup>d</sup> Data from Kello and Kostial (10).

tabolism of metals between sucklings and older animals became apparent (Table 2).

The whole body retention in sucklings was higher (2.3 times for lead, 1.4 for mercury, 1.1 for cadmium, and 3.2 for manganese) than in older rats although the differences were never as high as after oral administration of these metals.

Highest differences in organ retention were observed in the brain, where the percentage retention was 8 times higher for lead, 19 for mercury, and 28 for manganese in the postnatal period. The percentage in the blood was in sucklings 2 to 3 times higher for lead, mercury and cadmium and 6 times for manganese. In the liver, a 13-fold higher retention

was found for mercury, 2 times higher for manganese, and a slightly lower retention for lead and cadmium. The retention in the kidney was in the sucklings 2 to 3 times lower for mercury and lead and slightly higher for cadmium and manganese.

Differences in the retention and organ distribution of metals in the neonates could be anticipated on the basis of their physiological differences from adults. It is astonishing, however, that so few data are generally available on this topic [e.g., for cadmium (30), plutonium (31), americium (32), manganese (33)].

In our experiments, age-related differences were always observed, although experimental conditions

with regard to age of sucklings, age of older animals, route of administration, etc. were not identical for all the metals. Sucklings always showed a higher whole body retention, higher blood levels and a much higher retention in the brain. The explanation for these age related differences is speculative and mostly based on our insufficient knowledge of physiological processes in the postnatal period. This period is characterized by a high growth rate and a high rate of protein synthesis which could be the main reason for different handling of metals. The neonates are also believed to have a higher extracellular volume and a higher content of body water (4). A difference in the binding of metals to plasma proteins (4) or to body ligands in sucklings (34) could influence the values in blood as well as the metals, distribution and excretion from the body.

In the brain, great morphological changes are known to occur in the first month of neonatal life. A high concentration of free amino acids, whose functional significance is still unknown, and a higher body lipid mass have been found in the central nervous system (6). A higher permeability of the blood brain barrier is also assumed at this age (35). These conditions could cause a higher metal accumulation in the brain, which might be of special significance since the brain could be the "critical" organ for toxic metals in neonates.

The differences in the percentage retention of lead, cadmium, mercury and manganese in the blood, brain, liver, and the kidney were not high enough to account for the total increase in whole body retention of these metals in sucklings. Some other tissues must also be playing a role in this retention in the newborn (36).

## Toxicity

The highest oral toxicity was found in the youngest group of rats (two week-old sucklings) as indicated by the lowest LD<sub>50</sub> values for cadmium, mercury, and manganese (Table 3). In three and six

week-old animals a sharp decrease in toxicity was noted and in comparison to sucklings LD<sub>50</sub> values increased by a factor of 5, 3, and 2 for cadmium, mercury, and manganese, respectively. In adult rats the toxicity increased again and reached in the oldest animals values which were similar (manganese) or only little higher (1.4 times for mercury and 2.3 times for cadmium) than in sucklings.

The increase in the toxicity of metals in sucklings was not as high as expected on the basis of the very high intestinal absorption at this age. Goldenthal (37) has reported that oral doses of lead arsenate were only 1.5 times lower in sucklings than in adults. These data therefore do not support the hypothesis of an increased sensitivity to metals in the newborn. This is in agreement with our previous results on intraperitoneal toxicity of lead (38) when LD<sub>50</sub> values for lead acetate were the same for young and adult rats, although young rats retained about two times more lead than adults. Lin, Malaiyandi, and Romero-Sierra (39) found that LD<sub>50</sub> values for oral methylmercury in rats decreased with age, i.e., that younger rats tolerated higher doses of methylmercury, but their youngest group of rats was eight weeks old.

The lower sensitivity to toxic metals might result from a different binding of metals to ligands and a lower level of "free metal" in sucklings (34). Older rats might be more susceptible to metal toxicity because of a general decrease in adaptive responsiveness which is characteristic of the process of aging (40).

## Conclusion

Under conditions of an increased environmental exposure to toxic metals in the mother, the neonate is likely to have a body burden of the metals as the result of transplacental transfer (41). Our findings indicate that in the early postnatal period further accumulation of metals might occur as a result of a higher intestinal absorption and a higher body and organ retention. A higher body burden of toxic met-

Table 3. Toxicity of cadmium mercury, and manganese in rats in relation to age: LD<sub>50</sub> values 8 days after a single oral administration.<sup>a</sup>

Age, weeks	CdCl <sub>2</sub> LD <sub>50</sub> (95% confidence limits), mg/kg	HgCl <sub>2</sub> LD <sub>50</sub> (95% confidence limits), mg/kg	MnCl <sub>2</sub> LD <sub>50</sub> (95% confidence limits), mg/kg
2	47 (43-51)	35 (30-42)	804 (735-897)
3	240 (198-291)	105 (89-124)	1860 (1655-2009)
6	211 (182-252)	92 (77-108)	1712 (1553-1887)
18	170 (140-206)	50 (40-63)	850 (775-957)
54	109 (86-136)	50 (43-59)	619 (564-702)

<sup>a</sup> Six dose levels of each metal were used in each age group (6 rats were used for each dose level tested). Metal chlorides were applied by stomach tube in a volume of 1 ml/200 g of body weight. Sucklings, males and females; older rats, females.

als is highly undesirable during this period of intense growth and functional development, regardless of whether the neonate is found to be more or less sensitive to the effect of toxic metals. An attempt to relate concentrations of metals in the tissues with health effect parameters is even more difficult in the very young than in the adult since a latency period might take place before biochemical and morphological changes induced by metals would cause measurable health effects (42). Although most of our observations are based on animal experiments we can conclude that it is reasonable to consider the early neonatal period as a "critical" or "vulnerable" period for metal accumulation and therefore also for metal toxicity.

The possibility that toxic metals in the environment might cause harmful effects not only to present but also to future generations is becoming a matter of general concern (43). Most of the evidence of gametal, embryotoxic, fetal or neonatal toxicity of metals in humans or experimental animals has been obtained under extreme exposure conditions (1-3). Further work along this line is definitely needed. It is again to be expected that most of the future work will have to be performed on experimental animals. In planning these complicated multifactorial experiments an effort should be made to provide for chronic exposure (by the oral route or by inhalation) to metals in the chemical form and at the dose levels to be expected in the environment—as suggested for future cadmium research by Friberg et al. (44). The sampling of data should be performed at strictly determined "critical" periods over the entire developmental cycle in agreement with established principles in developmental pharmacology (45).

In this field, where gaps in our knowledge of physiological processes in the immature make the interpretation of the differences in metal metabolism and toxicity extremely difficult, only an organized international research effort is likely to give satisfactory answers to urgent problems in environmental metal toxicology.

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