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Reproductive and developmental toxicity of metals

by Thomas W Clarkson, PhD,¹ Gunnar F Nordberg, MD,² Polly R Sager, PhD³

CLARKSON TW, NORDBERG GF, SAGER PR. Reproductive and developmental toxicity of metals. *Scand J Work Environ Health* 11 (1985) 145-154. This paper discusses metal exposure in the male, the nonpregnant female, and the maternal-offspring unit. In the first two situations, the primary targets are the gonads. In the mother-offspring unit, consideration must be given to effects on the fertilized ovum, the growth of the embryo, and, finally, to the fetal and perinatal stages. The central nervous system may be especially vulnerable during development. The placenta also undergoes development, and either the placenta or the fetus may be the primary target. In humans, certain metals may cause abortion or other effects on the conceptus. Effects may also be produced by metal exposure both in utero and in the suckling infant. For example, methylmercury gives rise to a range of effects on the central nervous system at doses lower than those producing damage to the mature nervous system. Effects of lead and arsenic are associated mainly with postnatal exposures during infancy and early childhood, but there is reason to believe from animal experiments that some effects may occur from prenatal exposures to certain metal compounds.

Key terms: aluminum, arsenic, cadmium, chromium, fetus, lactation, lead, mercury, placenta, suckling.

The reproductive and developmental effects of metals were of considerable interest at the turn of this century, particularly with regard to the reproductive and developmental effects of lead. In fact, concern by physicians and public health authorities of that time more or less led to the exclusion of women from the workforce in lead-using industries. Interest in developmental and reproductive toxicity has revived dramatically in the last two decades or so for a number of reasons. The thalidomide disaster alerted us to the teratological effects of some chemicals. The outbreaks of methylmercury poisoning in Japan pointed to the possibility that prenatal life was the most sensitive stage of the life cycle to methylmercury. The poisoning of large numbers of children in homes using lead paints warned us of the dangers of the developmental effects of lead. For these and other reasons there was a blossoming of both experimental work and epidemiologic studies, looking for reproductive and developmental effects on exposed human populations. In the case of lead, epidemiologic studies of exposed children have now become a truly major activity with regard to the effects of this metal on human health.

There are also social reasons why interest in the reproductive and developmental effects of metals is increasing. In the first place, the movement that has occurred and is occurring of women into the workforce has raised once more the question of establish-

ing adequate protective guidelines for reproductive and developmental toxicity. Second, in many countries, there is now an increasing tendency to delay parenthood and thus extend the possibilities of exposure, and perhaps even susceptibility, to reproductive damage.

This report reviews the toxicology of metals with regard to both the reproductive system and the developing tissues. It is, in part, based on a conference held in the summer of 1982 and sponsored by a subcommittee of the Permanent Commission and International Association on Occupational Health. This committee, the Scientific Committee on the Toxicology of Metals, produced an extensive review of this field (9), and we will attempt to update this information. We summarize both the effects and metabolism of metals as far as reproduction and development are concerned. At the same time we try to illustrate, by specific examples, some of the toxic effects and metabolic peculiarities that are found in reproductive and developing tissues.

The format of this review carefully divides data obtained directly on humans from data experimentally derived from animals. One of the reasons for this separation is what appears to be substantial species differences in terms of both the effects and metabolism of metals. Also in this format we not only deal with a number of metals, but also with different chemical or physical forms of the same metal, as the speciation of the metal is also important in determining the toxicology. The first part of this review considers the effects of metals on reproduction and development. It is followed by a review of the metabolic fate of metals in developing animals, both prenatally and in the early postnatal period. We have deliberately limited this review to the suckling period and have not extended it to a later period in childhood since

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this extension would involve the enormous literature on lead which has been reviewed by many conferences within recent years. It would also require too much space for the purposes of a review of this kind, which has to deal with many different metals.

Effects on reproduction and development

Figure 1 summarizes the general results of experimental work on animals. The metals presented in this figure, and in subsequent figures of this type, represent those metals on which most work has been done with regard to effects on reproduction and development and with regard to metabolism. Work has occurred on a number of other metals but, in general, the vast majority of the metals in the periodic table that are not mentioned have received no attention.

It is clear from figure 1 that a considerable amount of work on animals has taken place with regard to prenatal exposure, that somewhat less work has occurred on looking for effects on the reproductive system in adults, and that there is scarcely any work on the effects of metals in neonatal and suckling animals.

The effects recorded from these experimental studies are many and varied. Effects on the reproductive system in adults relate mainly to effects on fertility, early embryonic or fetal loss, effects on spermatogenesis or estrous cycle, and to morphological effects on the gonads of the male or female animal. The effects arising from prenatal exposure have been selected mainly in terms of development, particularly the effects of the metal on the morphological development that might result in birth defects and gross terata, as well as more subtle effects on the develop-

ing animal, such as changes in the growth or maturation of the central nervous system. Fetal or maternal death caused by an exposure is not considered a developmental effect. In the few postnatal studies that have been carried out, the type of effects recorded is usually nonspecific, such as a failure of the suckling animal to gain weight or mortality of suckling animals. Only in the case of lead have more specific effects on the central nervous system been noted.

Some of the effects that have been observed in experimental work are highly specific to the metal, and the effect itself may be the only one recorded for the animal. For example, animals given parenteral doses of lead at specific periods during gestation may produce offspring that have highly specific skeletal abnormalities. Cadmium injected into adult male animals will produce dramatic damage to the testes but will affect no other tissue. Such effects are extremely interesting from the research point of view. Indeed, metals may be useful tools in helping us understand the mechanisms underlying the development and maturation of tissues such as, for example, the unique properties of the testes that make them sensitive to cadmium. The problem is that the majority of these experimental studies on animals are difficult to interpret with regard to potential risk to human beings. In many cases, the metal is injected or given by a route of exposure which is unlikely to occur in human beings. The nature of the exposure, such as the acute single dose, is unlikely to reflect the usual occupational or environmental exposure of human beings. The form of the metal, often a highly soluble salt in an aqueous solution, also probably does not relate to normal conditions of human exposure. In addition there are species differences in the teratogenic effect of chemicals that have been well documented over the last two decades. In general, therefore, we

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF METALS IN ANIMALS					
LIFE STAGE		ADULT		PRE NATAL	EARLY POST NATAL
Target		Reproductive System		Developing Tissues	Developing and Maturing Tissues
		Male	Female		
MERCURY	Vapor		3		
	Inorganic	15	18	12	
	Alkyl	15	18	9, 25	9, 25
	Phenyl				
LEAD	Inorganic	15, 16	16, 18, 26	9, 25	8, 25
	Alkyl		21	21	
ARSENIC	Inorganic III			9, 25	9, 25
	Inorganic V			9, 25	
	Alkyl			9, 25	
CADMIUM	Inorganic	15, 22	22, 18	9, 25	
CHROMIUM	Inorganic II	15		9, 25	
	Inorganic VI	15		9, 25	
NICKEL	Inorganic	15	18	9, 25	
	Carbonyl			9, 25

No Effect
 No Reported Effect
 Reported Effect
 Critical Effect

Figure 1. Experimental findings on reproductive and developmental effects of metals on animals according to the presence or absence of effects reported in the literature. "No reported effects" simply means that there are no reports in the scientific literature. The critical effects on animals are defined in the legend of figure 2, but it also implies that the experimental conditions provide a suitable model for humans. The numerals in the boxes indicate the literature sources. Review articles are usually quoted since space limitations do not allow quoting all the original references.

are not able to interpret most of these experimental results with regard to potential effects on humans.

The exceptions to this conclusion are indicated in figure 1 as critical effects. Normally, the term critical effects has been reserved for effects on humans only, those effects which, if prevented, would guard against serious hazard to the human exposed to the metal. For a full discussion of critical effects, see the report of Nordberg (20). The term critical effect, as far as experimental work is defined, is that effect which, if prevented, would guard against serious toxicity. Furthermore, the experimental conditions should provide an appropriate model for humans. The critical effect due to lead exposure in the suckling period refers to a well-established animal model in which suckling animals receive lead via breast milk from the exposed mother. The other two critical effects refer to experimental studies with methylmercury compounds. One report in the literature notes the effects of methylmercury on spermatogenesis in rats at a remarkably low dose of methylmercury, a dose that is about ten to one hundred times lower than doses associated with the well-known neurological effects of methylmercury. Unfortunately, there is only one report in the literature of this sort, and it certainly needs confirmation. The better documented critical effect of methylmercury is that due to prenatal exposure, as a variety of effects can be produced on the developing central nervous system by this form of mercury. In general, the effects of methylmercury are produced by interference with the normal processes of development and maturation of the central nervous system. These effects occur at doses considerably lower than those producing effects in adult animals. The route of exposure is not crucial with regard to comparison to human exposure inasmuch that methylmercury is

well absorbed into the blood stream no matter how it is administered.

The effects of metals on reproduction (4) and development in humans are shown in figure 2. In dramatic contrast to the experimental work in animals, it may be seen that reports on human studies are very few, particularly on effects on reproduction. Interestingly, two metals, namely, cadmium and organic arsenic, have been reported to produce no effect, in one case on the male reproductive system (cadmium) and in the other case in relation to prenatal exposures (arsenic). The absence, for example, of effects of cadmium on the testes in humans can be explained by the induction of metallothionein, which occurs on repeated exposure to cadmium and has been well described in the studies by Nordberg (19). This is an interesting example in which dramatic effects are seen when a metal is given as a single dose by the parenteral route to animals, as opposed to chronic exposure either by inhalation or oral intake in humans. The effects of lead recorded in this figure are difficult to evaluate from the point of view of whether they are critical or not since information on the dose and the duration of exposure is not very precise. It is known from clinical reports in the early literature that lead affects both the male and female reproductive systems. More recent studies in Scotland have suggested that prenatal exposures to lead may result in mental deficiency in children, and postnatal exposure to lead is well documented as a major public health concern with respect to children.

Cadmium is becoming of interest due to the possibility that it might affect placental structure and function, possibly at low doses. We have little information on this possibility at present; therefore no final decisions can be made as to whether this effect can be regarded as critical.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF METALS IN HUMANS				
LIFE STAGE	ADULT		PRENATAL	EARLY POSTNATAL
	Reproductive System		Developing Tissues	Developing and Maturing Tissues
Target	Male	Female		
MERCURY	Vapor	3		
	Inorganic			
	Alkyl		9, 25	9, 25
	Phenyl			9, 25
LEAD	Inorganic	15, 13	9, 25	9, 25
	Alkyl	21		
ARSENIC	Inorganic III			9, 25
	Inorganic V			
	Alkyl		9, 25	
CADMIUM	Inorganic	9, 25	9, 25	
CHROMIUM	Inorganic II			
	Inorganic VI			
NICKEL	Inorganic			
	Carbonyl

No Effect
 No Reported Effect
 Reported Effect
 Critical Effect

Figure 2. Reproductive and developmental effects of metals on humans according to the presence or absence of effects reported in the literature. "No reported effects" simply means that there are no known reports in the scientific literature. The critical effects, defined according to Nordberg (20), are the earliest effects which, if prevented, would guard against serious health effects. The numerals in the boxes indicate the literature source — usually a review article.

Methylmercury remains the only well-established, well-documented environmental teratogen in humans, in addition to the effects of radiation. Because of this documentation, and because it is a critical effect of methylmercury, we should like to illustrate some of the data that supports this conclusion.

Figure 3. Dose-response relationships for adult (a) and prenatal (b) exposures to methylmercury. (a) The relationship between the percentage of individuals complaining of paresthesia and the estimated maximum concentration of mercury in hair. The graph is taken from a report of an outbreak of methylmercury poisoning in Iraq. Hair concentrations used in this graph were calculated from blood concentrations reported by Clarkson et al (6) using a hair to blood concentration ratio of 250:1. It was noted (6) that maximum blood concentrations could have been higher by a factor of approximately two. (b) The relationship between the percentage of children experiencing motor retardation and the maximum mercury concentration in maternal hair during pregnancy. The graph is taken from Clarkson et al (8), who noted that the maximum hair concentration may have been higher due to possible misalignment of hair strands.

Humans exposed to methylmercury in utero can suffer severe damage to the central nervous system, as evidenced by the outbreak in Minamata, Japan, where children born of exposed mothers had severe cerebral palsy, whereas the mothers were hardly affected. As already indicated, this sensitivity of prenatal life has also been well demonstrated in animals. More recently, in the studies of the Iraqi outbreak and in certain native populations in Canada, it has become clear that methylmercury has more subtle effects on the human central nervous system that result in signs and symptoms of psychomotor retardation. These effects would appear to be the earliest prenatal effects of methylmercury. It is of interest to compare a dose-response relationship in adult versus prenatal exposures. Figure 3 illustrates the relationship, in adults, between the symptoms of paresthesia, which is usually the first symptom to appear in adults exposed to methylmercury, as a function of the concentration of methylmercury in hair. The hair concentration was used as a measure of the concentration in blood, the hair to blood concentration being relatively constant for methylmercury in human subjects (1). It may be seen in this "hockey stick" analysis that there was a low background frequency of paresthesia in this Iraqi population and that, at a certain point, the incidence of paresthesia due to methylmercury emerges above this background population frequency. The emergence above the background frequency appears at a hair concentration of about 100 $\mu\text{g/g}$. Also shown is the frequency of motor retardation in Iraqi infants that were prenatally exposed; plotted horizontally is the maximum hair concentration in the mother during pregnancy. The same general shape of the relationship is a hockey stick: a background frequency of a few percent quoted for this population, followed by an increase due to maternal exposure to methylmercury.

Figure 4. Effect of methylmercury (MeHg) treatment on cell mitosis in neonatal mice. Two-day-old mice were orally administered methylmercury at 4 or 8 mg of mercury (Hg)/kg of body weight. Animals were sacrificed 24 h later, and matched sections of brain were prepared. The total number of mitotic figures in the external granule layer of the cerebellar cortex was recorded and classified as early (prophase and metaphase) or late (anaphase and telophase). Data are reported as the percentage of late mitotic figures; bars are standard errors ($N = 10-15$). Mercury concentrations in brain for both males and females were 2.7 $\mu\text{g Hg/g}$ at the 8 mg Hg/kg dose and 1.8 $\mu\text{g Hg/g}$ at the 4 mg Hg/kg dose (adapted from Sager et al (24)).

In contrast to the adult data, this increase appears to be occurring at a lower hair concentration, possibly by a factor of ten lower than that seen in adults. It should be pointed out that there is considerable uncertainty in these estimates although the two lines are statistically significantly different.

The remarkable sensitivity of the developing central nervous system to methylmercury has stimulated a considerable amount of experimental work into the mechanisms underlying this sensitivity. Observations of tissues from both the Japanese and Iraqi outbreaks indicate that methylmercury can severely disrupt the normal developmental processes in the human brain. Evidence in the Iraqi outbreak suggested an interruption of the processes of neuronal migration. The finding of microcephaly strongly indicated that the growth of the brain itself and possibly cell division might also be affected.

Experimental studies on animals have indicated one important process affected by methylmercury, namely, that of cell division. In these studies, neonatal mice were given a single oral dose of methylmercury that resulted in mercury levels in the brain on the order of 1 or 2 $\mu\text{g/g}$. These levels are the lowest recorded to produce adverse effects either in animals or in man. These workers observed that the proliferating granule cells of the developing cerebellum underwent a remarkable inhibition of division, as indicated by the decrease in late mitotic cells. Figure 4 shows that this phenomenon occurs with both doses of methylmercury that were used, 8 mg of mercury/kg and 4 mg of mercury/kg. At the lower dose, one can also see a remarkable sex difference in sensitivity, the male animals being considerably more sensitive than the females. This finding is of considerable interest inasmuch that a recent epidemiologic study in Canada (11) claimed to find that males, in a Cree Indian population in Quebec, seemed to be more sensitive than females to psychomotor retardation related to prenatal exposure to methylmercury.

The working hypothesis proposed by Sager and co-workers is that methylmercury attacks the protein tubulin and thereby produces a destruction of micro-

tubule structures, including the mitotic spindle in neurons. The microtubules have a number of critical functions in the cell, including cell division and cell migration. Figure 5 illustrates the working hypothesis, that is to say, that, if tubulin is the molecular target for methylmercury, then the processes of both cell division and cell migration will be affected. This hypothesis is attractive inasmuch that both of these processes occur in neurons only in the developing central nervous system and thereby might provide an explanation for the increased sensitivity of the developing central nervous system versus that of the mature tissue.

Metabolism of metals in reproduction and development

The topic of the metabolism of metals includes information on the absorption, distribution, tissue deposition, and excretion of metals, as well as the metabolic fate of the metal such as oxidation, reduction reactions, and methylation or demethylation reactions in the body. The limited amount of data published in the literature to date, however, has led us to restrict the discussion to the transport of metal across the placenta and to the behavior of the metal in the suckling animal.

The transplacental movement of metals is summarized in figure 6. The available data are used to compare the levels in tissues or in the animal at birth with levels in the mother. It is recognized that this procedure is less than satisfactory because the movement across the placenta may change with the period of gestation and that the important information is probably the movement of the metal at periods well before the date of birth. Nevertheless, certainly with the human data, we are restricted to information comparing, for example, concentrations in cord blood to those in maternal blood.

Figure 6 shows that a great deal more work has been carried out on animals than on humans. For

Figure 5. Diagrammatic illustration of the "tubulin" hypothesis for prenatal effects of methylmercury [adapted from figure 11 of Clarkson (5)]. For details, see the text.

TRANSPLENTAL MOVEMENT OF METALS

METAL CONC RATIOS		FETAL TISSUES/MATERNAL TISSUES	
Data Source		Human	Animal
MERCURY	Vapor		9, 25
	Inorganic		25
	Alkyl	25	25
	Phenyl		25
LEAD	Inorganic	25	25
	Alkyl		
ARSENIC	Inorganic III		25
	Inorganic V		25
	Alkyl	25	25
CADMIUM	Inorganic	25	25
CHROMIUM	Inorganic III		25
	Inorganic VI		25
NICKEL	Inorganic		25
	Carbonyl		

Fetal / Maternal
Tissue

< 1.0
No reports
~ 1.0
> 1.0

Figure 6. Transplacental movement of metals, as indicated in terms of the ratios of the level in fetal tissues to the corresponding levels in maternal tissues at the time of birth. For humans, the ratio of the concentration in cord blood to the concentration in maternal blood was used. The numbers in the boxes indicate the data source. (conc = concentration)

Figure 7. Relationship between the concentration of mercury in blood in newborns and the simultaneous concentration in maternal blood in a population exposed to methylmercury in fish. Whole blood concentrations are approximately one-half the concentration in the red blood cells. The data are taken from Skerfving (26).

certain metals, such as trivalent chromium, cadmium, and inorganic mercury, the animal work indicates that passage across the placenta into the fetus is virtually nonexistent. A number of other metals cross the placenta such that fetal levels at birth are approximately equal to those in the mother. The three forms of mercury (methylmercury, phenylmercury, and mercury vapor) (10) have an unusual predilection to cross the placenta and accumulate in fetal tissue. It is of interest that, although there is now substantial evidence from animals that inhaled mercury

vapor can produce higher levels of mercury in the fetus than in the mother, very little, if any, work on animals or humans has been carried out to look for prenatal effects of mercury vapor.

Methylmercury is well documented as crossing the placenta readily and accumulating in fetal tissues. Figure 7, taken from work by Skerfving (26), demonstrates that, in fish eaters, levels in cord blood at birth are substantially higher than those of maternal blood and that the proportion in fetal blood versus maternal blood holds over a wide range of concentrations. This distribution of methylmercury is, of course, consistent with the critical effects on the developing nervous system.

Published information on the metabolism of metals in suckling animals is summarized in figure 8. The paucity of data is clearly evident. Interestingly, slightly more information is available on humans than on experimental animals. We have attempted to summarize the available information in terms of whole-body accumulation, that is, to assess the processes of absorption and of excretion of the metal as they affect whole-body accumulation. For example, it is now established, in both humans and animals, that cadmium is absorbed from the immature gut of the suckling animal to a much greater extent than in the adult; therefore it is indicated here as a process that tends to increase whole-body accumulation as compared to absorption in adults. There rates of excretion of methylmercury and inorganic mercury are much lower in the suckling animal than in the adult; these are therefore indicated as processes that will lead to higher accumulation than in the adult. It is of interest that with only one exception — methylmercury absorption — all the processes that have been looked at to date in suckling animals point to increased accumulation at this stage of the life cycle as com-

METABOLISM IN SUCKLING OFFSPRING

END RESULT		WHOLE-BODY ACCUMULATION			
PROCESS		ABSORPTION		EXCRETION	
Data	Source	Human	Animal	Human	Animal
MERCURY	Vapor				
	Inorganic		9, 25, 14		27
	Alkyl		9, 25		23
	Phenyl				
LEAD	Inorganic	17	9, 25		
	Alkyl				
ARSENIC	Inorganic III				
	Inorganic V				
	Alkyl				
CADMIUM	Inorganic	17	14		
CHROMIUM	Inorganic III				
	Inorganic VI				
NICKEL	Inorganic				
	Carbonyl				

No Reports
 Body Burden As Compared to Adults
 Reduced
 Similar
 Greater

Figure 8. Metabolism of metals in suckling offspring is presented as a consideration of the effect of the processes of absorption (oral) and excretion on the body burden of the metal in the suckling animal as compared to that of the adult. For example, an oral dose of cadmium is absorbed from the gastrointestinal tract to a greater extent in the suckling than in the adult animal. Thus the box is labeled to indicate a greater body burden in the suckling animal as compared to an equivalent oral dose in the adult. The data source for each box is indicated by the reference numeral.

pared to the adult. It is therefore astonishing that so little work has been carried out in this area.

The situation with regard to inorganic mercury is particularly intriguing. Mercury in the inorganic form is much more efficiently absorbed from the gastrointestinal tract in suckling animals than in adults (approximately 50 % absorption versus 5 % in adults). Moreover, the suckling animal lacks the ability to excrete inorganic mercury so that the combination of these two differences between suckling and adult animals would suggest a very considerable potential for accumulation during the suckling period. There is anecdotal and rather brief clinical information suggesting that, indeed, inorganic mercury can affect the human infant, but to date no careful study has been carried out, either on animals or on man, using inorganic mercury at this stage of the life cycle.

Information on methylmercury is more substantial. Methylmercury is well absorbed, up to 95 %, in the adult, as well as in the suckling animal. However, as in the case of inorganic mercury, the suckling animal lacks the ability to secrete methylmercury. This lack is demonstrated in figure 9. Animals dosed with methylmercury at 2 d after birth did not excrete any of the metal during the suckling period, whereas animals dosed at 24 d of age, just after weaning, excreted methylmercury at the normal adult rate. There is, therefore, a very dramatic increase in the excretion process at about the time of weaning.

Figure 10 illustrates current knowledge on the role of the enterohepatic cycle in the absorption and excretion of methylmercury in animals. In this diagram, oral intake of methylmercury is represented as occurring at 100 units/d. The majority of the ingested methylmercury is absorbed, carried via the portal circulation to the liver. There, part of the methylmercury is distributed to the remaining tissues in the

Figure 9. Ontogenic changes in the excretion of methylmercury in male mice. Groups of male mice received a single oral dose of methylmercury chloride (0.4 mg of mercury/kg) labeled with the ^{203}Hg isotope. The body burden was determined by whole-body counting. The dose was given at 2 d of age ($\blacktriangle$) or at 24 d of age ($\bullet$) [adapted from figure 1 of Rowland et al (23)].

body, and part is secreted in the bile, where it is either reabsorbed or becomes a substrate for the gut flora which convert methylmercury into inorganic mercury. The inorganic form, thus produced, is poorly absorbed, about 5 to 10 %, so that the vast majority of the inorganic mercury is excreted in the feces. Fecal excretion accounts for approximately 90 % of the total excretion of mercury, and virtually all of the mercury is excreted in the inorganic form in feces and urine. The numerals indicated in this diagram correspond to a steady-state situation in man where intake

Figure 10. A schematic representation of the absorption and excretion of methylmercury (CH_3Hg) in man with special emphasis on the pathway of fecal excretion. It is assumed that a human adult has achieved a state of balance whereby 100 units of methylmercury are ingested daily and 100 units excreted (90 in feces, 10 in urine). The whole-body accumulation is 10 000 units based on a whole-body half-time of 69 d. A large enterohepatic circulation is assumed whereby some 385 units pass into the intestinal tract and become exposed to intestinal microflora which demethylates part of the methylmercury to inorganic mercury (Hg^{++}). The latter is only slightly absorbed and most is secreted in the feces. Thus the two important sequential steps leading to fecal excretion are (i) biliary secretion of methylmercury and (ii) microbial demethylation in the gut [adapted from Clarkson et al (7)].

Figure 11. Ontogenic changes in the biliary secretion of methylmercury and reduced glutathione in developing rats. An intravenous injection of mercury (1 mg/kg) as methylmercury chloride (CH_3HgCl) labeled with the ^{203}Hg isotope was given to 14-day-old, 21-day-old, and 28-day-old rats, and bile was collected every hour for 4 h. The group size was between 8 and 12 animals. The secretion rates were those measured 3 h after the mercury administration. For further details, see the report of Ballatori & Clarkson (2).

Figure 12. Ontogenic changes in the rate of in vitro demethylation and in the excretion of inorganic mercury. The in vitro demethylation was measured by suspending the colon contents (10 % weight/volume) in culture medium (pH 7.0) and incubating under anaerobic conditions with methylmercury chloride (CH_3HgCl) (0.5 $\mu\text{g}/\text{ml}$) at 37°C . The cumulative fecal excretion of inorganic mercury was measured in mice given a single oral dose of CH_3HgCl (0.45 mg of mercury/kg) and collecting the feces over 8 d [adapted from table 1 and figure 2 of Rowland et al (23)].

is balanced by excretion. With a biological half-time of approximately 70 d in man, it predicts that the total body burden in man is about 100 times the daily intake. The important excretion mechanisms illustrated are (i) the biliary secretion of methylmercury and (ii) the breakdown of methylmercury to the inorganic, nonabsorbable form. The question arises as to whether these two processes are different in suckling animals and therefore leads to the lack of fecal excretion.

Studies by Ballatori & Clarkson (2) indicate that the biliary secretion process is very much reduced in the suckling animal, as indicated in figure 11. It may be seen that the 14-day-old rat has a much reduced capacity to secrete methylmercury in bile as opposed to the 21-day-old, and to the 28-day-old animal which is secreting methylmercury in bile at practically the adult rate corrected for body weight. It is of interest that the amino acid glutathione, which is known to bind methylmercury in bile, also shows this ontogenic difference in excretion. In fact it is this finding that strongly suggests that the secretion of methylmercury in bile depends upon the secretion of this SH-containing amino acid.

However, biliary secretion of methylmercury is not the only process depressed in the suckling animal. Rowland and his colleagues (23) have reported that microflora in the suckling animal lacked the capacity to demethylate methylmercury, as indicated in figure 12. Two types of studies were carried out. Measurements of the *in vitro* demethylation of methylmercury by isolated gut flora indicated that gut flora taken from 10-day-old animals lacked the capacity to demethylate mercury as compared to that of 20-day-old animals. At the same time, the capacity of these animals to secrete inorganic mercury when given methylmercury also closely paralleled the demethylation rates in that the 10-day-old animals virtually lacked the capacity to excrete inorganic mercury, whereas the 20-day-old animals excreted inorganic mercury. Thus, it seems that the failure to excrete methylmercury in suckling animals results from a failure of both processes — biliary secretion as well as demethylation.

Conclusions

The increasing interest, both from the occupational and environmental viewpoints, in reproductive and developmental toxicity is illustrated by the increasing number of monographs being published in the last two to three years. This review of the topic with regard to metals has illustrated that the amount and type of information available is very different from one metal to another. In fact, there are very few metals on which we have any information at all.

Methylmercury is perhaps the best studied metal in this area. Surprisingly, mercury vapor and inorganic mercury, the two forms of mercury to which people

are occupationally exposed, have received very little attention despite the fact that animal work suggests that effects might be expected at least in certain times in the life cycle, such as the suckling stage. Lead is certainly a metal of concern, indeed as it was at the beginning of this century, but we are still lacking important information on the dose of lead, the blood levels of lead, and the periods of exposure to lead, which might result in reproductive and developmental effects. On the other hand, cadmium does not seem to present a broad range of reproductive and developmental effects, but there is now some interest in the possibility, currently based mainly on animal experiments, that cadmium, at rather low doses, may affect the structure and function of the placenta.

The experimental work on animals should be used at least to alert us to the possibility of effects on humans. Unfortunately, even for animals, many studies are still lacking. However, for vapor, metallic, and inorganic mercury, data from animal studies indicate that we should focus on human exposure in the developmental period. Remarkably little attention has been given to the neonatal and suckling period, in either humans or animals, despite the fact that metabolic evidence suggests that this could be a sensitive period of the human life cycle to certain metals.

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