Perinatal Exposure and Teratological End-points: Some Principles and Possibilities

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1 INTRODUCTION

Prenatal exposure to toxic environmental chemicals could affect male or female germ cells, or the various somatic organs. Goals for reproductive screening of potentially toxic chemicals are to determine the magnitude of possible germ cell or somatic damage and to estimate resultant impact on reproductive capacity or somatic functional capacity throughout the life cycle. Prenatal exposure to toxic chemicals could result in sterility or spontaneous abortion, reducing overall fertility. Even more worrisome, however, are lesser somatic effects which allow survival of individuals with varying degrees of mental and physical handicap or reductions in physiological adaptive capacities, who are, or will become, significantly handicapped during their lifetimes.

Concepts of normal and abnormal early mammalian development that may contribute to prenatal and postnatal reproductive screening strategies are briefly reviewed. Possible teratological and toxic effects of chemical agents on the developing organism must be evaluated within the context of rather extensive embryofetal, perinatal wastage and postnatal developmental and reproductive morbidity due to other environmental and genetic causes. Multiplication and differentiation of functional units during early development and effects on functional reserve adaptive capacity in the developmentally mature organism provide a conceptual framework for evaluating adverse effects of chemical agents.

The importance of valid dose–effect, dose–response relationships as an essential basis for hazard evaluation is stressed and is illustrated with the few available human examples.

Finally, lactation as a route of exposure is discussed because it represents a unique early postnatal nutritional stage during which the rapidly developing suckling infant is completely dependent on mother’s milk, which, if contaminated with toxic pollutant chemicals, could pose a significant threat to early postnatal growth and development.
BIOLOGICAL ASPECTS OF HUMAN DEVELOPMENT
RELATING TO EVALUATION OF ADVERSE REPRODUCTIVE EFFECTS OF CHEMICALS

During the course of normal prenatal human development the human conceptus increases from one cell, the fertilized egg, to \( \sim 1000 \) billions of cells in the newborn infant. From this quantitative dimension alone, to say nothing of the qualitative complexities of differentiation and interaction of at least \( 100 \) histologically distinguishable types of cells, it is not surprising to find that abnormalities of development are frequent. There is great opportunity for interference with early developmental processes due to abnormal intrinsic (genetic) capacity, as well as from adverse environmental influences (e.g. chemical pollutants) which may impact the developmental sequence. We have very little knowledge of details of developmental processes or the mechanisms by which they are impeded.

With this developmental perspective, it is not so surprising to learn that a large fraction of embryos and fetuses fail to develop with sufficient capacity to survive to birth. Recent clarification of the major contribution of chromosomal causes of early embryofetal wastage has provided insight that fetal incapacity due to chromosomal abnormalities and malformations of unknown cause contribute a large fraction of embryofetal wastage due to inability of abnormal embryos and fetuses to survive. In addition to the 15–20\% of pregnancies which end in perceived spontaneous abortions, it is currently estimated that 40–50\% of total conceptions do not survive to live birth, a phenomenon that is also observed widely in other mammalian species (Carr, 1977; see Warburton, this publication). Yet this extensive prenatal biological filtering by spontaneous abortion is not complete. Approximately 1 in 200 newborns has a detectable chromosomal abnormality, and it is conservatively estimated that 3–5\% of human infants are born with medically significant birth defects or mental retardation. Yet, there are few proven human teratogens and it has been predicted that drugs and environmental chemicals cause less than 1\% of congenital malformations (Wilson, 1973; Brent and Harris, 1976). A measure of the primitiveness of current knowledge is the admission that we are unable to assign specific causes for 60–70\% of malformations observed in human infants at birth (Wilson, 1973). Since most birth defects are of unknown aetiology it is possible that some additional portion could be due to prenatal exposure to toxic chemicals.

Approximately 3\% of the US population is considered mentally retarded (IQ \(< 70\)). About 10\% of these individuals are severely retarded (IQ \(< 50\)). It is currently thought that the majority of severe mental retardation represents discontinuous phenotypes due to chromosomal, environmental, Mendelian and multifactorial causes (Opitz, 1980). The numbers of mild to moderately retarded persons who may have been adversely affected by prenatal or perinatal exposure to toxic environmental chemical agents cannot currently be estimated. Recently, the first strong evidence has been presented that childhood (non-occupational)
exposure to unidentified ambient sources of lead can cause neuropsychological deficits that may interfere with classroom performance (Needleman et al., 1979, 1982). The frequency of non-adaptive classroom behaviour increased in a dose-related fashion relative to dentine (tooth) lead levels, at doses below those producing signs or symptoms severe enough to be diagnosed clinically.

To evaluate possible adverse effects of prenatal chemical exposure, toxic effects of chemicals must be distinguished from the rather high background frequencies of prenatal growth retardation, birth defects, mental retardation and learning or other behavioural disorders of unknown cause. The formidable task of determining valid dose-response relationships in prenatally and perinatally exposed populations has infrequently been accomplished to date. Exceptions are the dentine lead–school performance study of Needleman et al. described briefly above, and the Iraqi methylmercury outbreak described in more detail below.

Animal models provide powerful tools for investigating mechanisms of teratological effects but currently applied teratogenicity tests seems very limited in terms of their capacity to predict human teratogens (Brent, 1972). Lack of fundamental knowledge of mammalian developmental biology is the most serious handicap we face in designing rational and reliable non-human reproductive screening tests. Thus present approaches to teratogenicity and developmental toxicity testing must be empirically derived. This situation could be improved by informative comparative pharmacokinetic studies among mammalian species as promoted by Rall and others (Freireich et al., 1966) coupled with further development of more sensitive structure–function assessment of postnatal end-points such as as those described by Rodier (see below). However, as commented by Wilson (1977): 'The absence of embryotoxicity in a well-conducted animal study, at doses representing reasonable multiples above estimated environmental levels, does not assure the safety of any chemical.'

Ultimately, direct observational studies in human populations must provide the most reliable test of whether or not exposure is associated with adverse health effects in humans. Possible end-points include a spectrum of effects from sterility, reduced fertility or spontaneous abortion or stillbirth, through intrauterine growth retardation, to survival with non-lethal congenital malformations or with aberrant or reduced functional capacities of various organs, especially the reproductive system or the central nervous system.

Stein and coworkers argue persuasively the importance of constructing pre-experiment design and evaluating post-experiment interpretation of environmental health studies of chemical agents in terms of statistical power analysis (Strobino et al., 1978; see Warburton, this publication). Power is a measure of the capacity of a study to detect an effect. Most observers would support extension of well-designed epidemiological surveillance studies to monitor possible effects of environmental chemical agents potentially injurious to exposed subsets or in some instances possibly to the population at large (see PCBs below). However, it must be emphasized that none of the major human teratogens has been identified by epidemiological methods (Miller, 1970), or by screening for
Methods for Assessing the Effects of Chemicals on Reproductive Functions

3 TOXIC OR TERATOLOGICAL EFFECTS ON FUNCTIONAL UNITS AND RESERVE ADAPTIVE CAPACITY

Concepts of development and regulation which have been originated or promoted by Goss (1964, 1966, 1978a, b) have potentially significant implications for understanding and evaluating teratological and toxicological effects of environmental chemicals on developing mammals. Goss' classification of tissues in terms of their mitotic or regenerative growth capacities provides a relevant general developmental framework.

Renewing tissues such as the epidermis, mucosal epithelium of the gut, seminiferous epithelium of testis, and blood cells, are in a continual state of multiplication, i.e. cellular losses are kinetically balanced by replacements (Figures 1, 2). For example, approximately one million new erythrocytes are constructed every second to replace an equivalent number which are destroyed during the same time interval. The germinative zones of these tissues, spatially distinct from the resultant differentiated cells, are populated with

![Diagram of tissue types](image)

Figure 1 Alternate pathways of growth and differentiation in tissues and organs. Renewing tissues continue to proliferate throughout life, generating descendants that differentiate into non-mitotic cells. Static tissues permanently lose the capacity to divide as they differentiate early in life; thereafter they grow by hypertrophy. Expanding tissues do not stop dividing until body growth ceases, despite their fully differentiated condition. (Reproduced with permission from Goss, 1967)
relatively undifferentiated progenitor ('stem') cells in a state of constant proliferation.

In expanding tissues such as most endocrine glands there is no spatial incompatibility between proliferation and differentiation. Dividing cells are diffusely distributed. There is no need for a germinative compartment separate from differentiated cells since all cells apparently are capable of division.

Mitotically static tissues, e.g. the nervous system and striated muscle, do not proliferate beyond early stages of development when neuroblasts and myoblasts begin to differentiate into neurons and muscle fibres. Cells of these static tissues, like those in expanding organs, are capable of living as long as the organism as a whole survives. Differentiated cells of both static and renewing tissues cannot divide. In static tissues the germinative cell population compartment is separated
from the differentiated cells in time; in renewing tissues, the separation is spatial.
In contrast to the inability of differentiated cells to renew and static tissues to proliferate, differentiated cells in expanding tissues have the capacity to proliferate with ease at all stages of the life cycle.

Proliferation of individual cells is sufficient to promote full functional competence of a tissue or organ only when the unit of function is the cell. Goss (1964) defines a functional unit as the smallest irreducible structure still capable of performing the physiological activities specific to the tissue or organ. Functional units may be single cells, e.g. blood cells or cells of many of the endocrine glands. Growth in these tissues involves production of new individual cells. Organs such as thyroid glands, or exocrine glands, have apparently retained unlimited capacity for producing new follicles, or secretory acini, and are therefore capable of remarkable growth and regeneration. Organs with this type of growth and regenerative capacity are referred to as indeterminate organs.

In some organs functional units are multicellular and they cannot be increased simply by multiplication of their constituent cells, although such cell multiplication can result in enlargement of individual functional units and in a limited increase in functional capacity. It would seem to have been to the advantage of the organism if such organs were capable of proliferating (or regenerating) at the organizational level of their functional units, yet the evolutionary sequence has eliminated regenerative capacity. Some organs such as the mammalian kidney are unable to increase their numbers of multicellular functional units. The number of nephrons in the kidney is fixed early in life and cannot be increased after developmental maturation (Figure 3). Compensatory growth of a kidney after removal of the other kidney of a pair is achieved by cellular hyperplasia and hypertrophy, resulting in larger nephrons with some increase in functional capacity, but mature kidneys are unable to regenerate nephrons. Organs incapable of regenerating functional units after maturity include lung (alveoli), small intestine (villi) and testes (seminiferous tubules) (Figure 3). Growth is possible in these determinate organs only by increasing size but not number of functional units.

It is apparent that toxic chemical agents (or other adverse genetic or environmental factors) could reduce total reserve adaptive capacity of determinate organs (1) by interfering with formation of the absolute number or anatomic distribution of functional units generated during early development, or (2) by destroying functional units after maturity when they can no longer be replaced. Both effects permanently reduce reserve capacity and render the organism liable to debilitating or even life-threatening effects if the numbers of functional units are further depleted by other physical, chemical or biological injurious influences, or by aging.

Thus, if an organ (indeterminate) can multiply its functional units it is capable of unlimited growth (hyperplasia) and regeneration to maintain functional efficiency. Conversely, determinate organs can compensate for developmental
reductions or mature losses of functional units only to a limited extent by enlarging the remaining functional units (hypertrophy). It is not yet apparent why certain organs are endowed with unlimited powers of growth while some of the most vitally essential organs of the body, the brain, the heart, the lungs and the kidneys, cannot augment their specified populations of functional units (Goss, 1967). Therefore, it is not surprising that these determinate organs, indispensable for survival, are susceptible to effects of adverse environmental effects which sooner or later may contribute to debilitation or lethality.

I do not mean to imply that there are not other important mechanisms for causing permanent injury to organs of developing mammals. Damage to the genome or interference with cell–cell interactions both during development and in the mature central nervous system are important possible mechanisms of teratological and structural toxic effects at the cellular or organ level. Nevertheless, if cells or functional units are not initially generated or are
324 Methods for Assessing the Effects of Chemicals on Reproductive Functions

destroyed and cannot be replaced, the possibilities for other levels of developmental or functional interactions have been eliminated.

We need to explore in a more enlightened way the potential of these concepts of genetically programmed development of functional units, determinate and indeterminate growth, and reserve adaptive functional capacity, as they could relate to investigating, understanding and preventing teratological and toxic effects of chemical (or other) agents on the developing mammal. They provide a powerful conceptual framework for quantitative assessment of structure (numbers of functional units) and function (physiological reserve capacity) relationships throughout the life cycle.

4 BEHAVIOURAL EFFECTS RESULTING FROM PRENATAL EXPOSURE TO TERATOGENIC AND TOXIC CHEMICALS

It is the hope of behavioural teratologists that the opportunity for examining a wide range of functional activities and responses after exposure to potentially toxic chemical agents will provide possibilities for discerning subtler effects than may be apparent by standard gross anatomical or histological analysis. Behavioural tests can be thought of as potential integrators of functional effects of possible minor structural abnormalities in many anatomical locations, which may be more difficult to discern by direct histological examination.

Adverse reproductive effects may include fetal death or gross malformation. Postnatal survivors can have residual gross or minor malformations, but other individuals may have subtler physical defects, or functional brain deficits expressed as reduced intelligence or aberrant behavioural responses, which would not be discerned by prenatal evaluation. Postnatal evaluation of effects of potential teratogens in animals is an important screening objective, since it is mainly this class of adverse effects, resulting in handicapped human survivors, which is of major concern to society.

Significantly abnormal function of most critical organ systems is usually expressed in mortality data. Physiological deviations compatible with survival require more demanding efforts to discern. Failure or impaired function of reproductive organs and impaired higher functions of the central nervous system are better tolerated than deficits in most other organ systems, since they have less drastic direct impact on survival of the individual. Therefore, these organ systems, especially the central nervous system, provide sensitive useful indicators of adverse effects of chemical agents.

The developing mammalian central nervous system is especially vulnerable because of its long developmental sequence continuing throughout much of embryofetal development and extending well beyond birth into infancy. While neurogenesis is only one of many complex events in the development of the nervous system, it is critical, for a nervous system lacking a full complement of neurons would not be expected to develop and function normally.
Figure 4 Chronology of proliferative bursts of neuron production in mouse CNS. Vertical line on E12 (prenatal day 12) represents last day of gestation when gross external malformations can be induced by interference with cell proliferation. Vertical line on day 19 represents time of birth. Parentheses enclose structures or cell type included as examples: for example, many thalamic nuclei are forming on E14—the medial nuclei are representative of a larger group. (Reproduced with permission from Rodier, P. M., 1980)
Methods for Assessing the Effects of Chemicals on Reproductive Functions

Through use of autoradiographic labelling techniques, complex schedules of production of different neuron types have been determined to occur over a long developmental period with bursts of different neuron types forming at different times (Figure 4) (see review by Rodier, 1980, for details). Thus the detailed

Figure 5 Hyperactivity. A variety of agents lead to hyperactivity of treated offspring when delivered during the period marked by stippling. (Reproduced with permission from Rodier, P. M., 1980)
chronology of production of different geographic populations of neurons becomes important for understanding the clinical relevance of timing of brain injury during development. Though absolute time schedules of the generation of neuron populations differ among mammals, relative temporal sequences of production of different types of neurons are similar.

Brain damage resulting from interference with neuron proliferation may have

Figure 6 Hypoactivity, reflex delays, locomotor abnormalities. Critical period for syndromes combining hypoactivity with various reflex delays and motor abnormalities is biphasic. Both early and late insults seem to lead to these behaviours, while insulfs in between these periods have other effects. (Reproduced with permission from Rodier, P.M., 1980)
a variety of behavioural effects, since the systems that are damaged will differ from one developmental stage to another. Studies of specific temporal insults (exposures to X-irradiation or azacytidine) to cell proliferation have documented that the behavioural effects are as time dependent as the corresponding neuroanatomical effects (Hicks and D’Amato, 1961; Rodier and Gramann, 1979). Cell loss at different times produces different behavioural effects. Rodier (1980) has related critical periods for behavioural effects to critical periods for neuron production using azacytidine to interfere with proliferation of neurons over short time intervals. Hyperactivity seems to be indicative of brain damage during the middle part of neuron production (Figure 5). In contrast, hypoactivity appears to be the result of interference with proliferation of neurons of cerebellum (Figure 6) either during the twelfth day of gestation or during the first postnatal week. Other timed prenatal insults produce abnormal performance on a variety of tests which involve learning (see Rodier, 1980, for further details). Thus it can be concluded that systemic insults at different stages of neurogenesis during brain development may result in significant and lasting behavioural alterations while leaving the affected animals apparently normal in physical appearance. The variety of behavioural effects that can be produced is extensive, even with the use of a single teratogen at different times during brain development. Timing of exposure and temporal sequences of proliferation of specific brain cell populations are obviously critical variables which govern the production of specific behavioural teratologies. Chemical agents which produce permanent alterations of behaviour must be regarded as hazardous even when they cannot be shown to produce morphological changes.

5 DOSE–EFFECT, DOSE–RESPONSE RELATIONSHIP—BASIS FOR HAZARD EVALUATION

Recently, Wilson (1977) wrote: ‘To date only one chemical agent in the nature of an environmental contaminant or pollutant has been established as embryotoxic in man, namely methylmercury, which causes both prenatal and postnatal toxicity.’ Methylmercury is also one of the few toxic environmental chemical agents for which a valid adult dose–response relationship has been determined. More recently, a dose–response has been measured for human prenatal exposure, providing important new information on which to base human hazard evaluation (Clarkson et al., 1981).

Large outbreaks of mercury poisoning in Japan in Minamata during the 1950s, and in Niigata in the 1960s, raised public concern about health hazards of methylmercury. The poisonings were caused by consumption of fish that had been contaminated by industrial discharge of methylmercury compounds (Tsubaki and Irukayama, 1977). When Swedish investigators discovered that inorganic mercury could be methylated by microorganisms in the environment to form methylmercury it was realized that the ecotoxicological threat was more
widespread (WHO, 1976; NAS, 1978). Standards for maximum safe levels of
methylmercury in edible fish were proposed by several nations, and WHO
advised a tolerable weekly intake of methylmercury (WHO, 1972, 1978). These
estimates were derived from best available data but there was an important need
for quantitative human dose–effect, dose–response relationships and for
identification of the most sensitive stage of the human life cycle. In Japan, it had
been observed that asymptomatic mothers exposed to methylmercury during
pregnancy could produce neurologically damaged offspring.

An unusual opportunity to obtain data for determining dose–response
relationships was provided when a large outbreak of methylmercury poisoning
occurred in Iraq during the winter of 1971–2 (Bakir et al., 1973). Within
approximately a 3-month period large numbers of rural families consumed
homemade bread prepared from seed wheat which had been treated with a
methylmercury fungicide. More than 6000 persons were hospitalized and
approximately 450 hospital deaths were attributed to methylmercury poisoning.
Many other individuals are known to have been seriously poisoned. The
importance of this large outbreak as a unique opportunity to obtain detailed
information on effects of prenatal exposure was appreciated and long-term
studies were initiated to document both adult and prenatal fetal exposures and to
observe toxic effects in resulting offspring.

Figure 7 The relationship between frequency of signs and symptoms and the estimated body burden of methylmercury. Both scales of the
abscissa refer to body burdens of methylmercury (mg) at the cessation of exposure. The two scales represented different methods of calculating the
body burden as discussed in the text. (Adapted from Bakir et al., 1973)
Dose–response relationships imply cause–effect relationships. Their importance as a basic input for human hazard evaluation is well recognized. The relationship between frequency of signs or symptoms and estimated body burden of non-pregnant adults in Iraq are shown in Figure 7 (Bakir et al., 1973).

It was discovered that the concentration of mercury in hair at the time of its formation is directly proportional to simultaneous concentration in blood. Sequential, segmental analysis of hair mercury content provided a reliable, quantitative means of recapitulation of exposure for 2 years or longer prior to the time of hair sampling, since hair grows approximately 1 cm each month. Maternal hair mercury levels were determined through pregnancy intervals, providing an integrative index of fetal exposure, and enabling dose–response relationships to be developed for postnatally observed effects of fetal exposure (Figure 8). Maternal hair mercury levels were related to frequencies of motor retardation and other central nervous system signs in 82 mother–infant pairs (Figure 9) (Clarkson et al., 1981).

These observations provide the first example of a dose–response relationship of human prenatal exposure to a toxic environmental chemical pollutant. The
adult and prenatal dose–response relationships enable quantitative comparison of differential sensitivity at different life cycle stages, providing a more sound basis for human hazard evaluation.

From these dose–response relationships EC50 values have been calculated which indicate that the human fetus is more sensitive to methylmercury than the
adult, non-pregnant person (Clarkson et al., 1981). Current estimates indicate roughly a factor of three or four in relative sensitivity. It should be pointed out that the slopes of the dose–response relationships for fetus versus adult are not parallel, so that different values of relative sensitivity are obtained if comparisons are based on body concentrations at other response frequencies. However, these data can be used to estimate practical thresholds which can help in setting limits for acceptable methylmercury exposures in other populations potentially at risk. Thus mercury studies in animals and in exposed human populations are providing required information for setting reliable environmental and nutritional intake limits.

6 CHEMICAL CONTAMINATION OF HUMAN BREAST MILK

Following birth the human newborn remains highly dependent on maternal sustenance and under normal biological circumstances receives total nutritional intake from breast milk for many months. Pollution of human milk with widespread synthetic chemical contaminants raises concern for potential adverse health effects on the rapidly developing, and presumed susceptible, suckling infant (Rogan et al., 1980).

Human breast milk is widely acknowledged to be the preferred food for human infants, even though formula-feeding by bottle is an acceptable alternative with apparent safety and good nutritional results in a majority of cases. Therefore, some alarm has been generated by the realization that human milk has often been found to contain a variety of lipid-soluble pollutant chemicals which are now known to be widely dispersed in the environment. Questions have been raised about the possible risk to infants suckled by mothers whose milk contains measurable quantities of a variety of synthetic organohalides such as the polychlorinated biphenyls (PCBs) and dichlorodiphenyl trichloroethane (DDT) (Barr, 1981).

Long-term low-level exposure to the organohalides results in gradual accumulation of residues in body fat, including the fat of breast milk (Rall, 1979). Lactation is the only route by which large amounts of such residues are known to be excreted. The fat content of breast milk varies widely among women, with some differences even in the same lactating mother from day to day, as well as significant increases in concentration even during a single feeding. Since these chemicals are nearly all partitioned in fat it is not surprising that there is considerable variation in reported milk levels. Concentrations of chemical residues in milk should be expressed on a fat content basis to aid in comparing results from different studies and over time.

A systematic survey of pesticides in mother's milk was sponsored by the Environmental Protection Agency (Savage, 1977). Of 1038 milk samples, 30% had levels above 0.05 parts per million (p.p.m.) on a whole milk basis, and 6.7% had levels above 0.1 p.p.m. More recently, breast milk samples from more than a
thousand nursing mothers in Michigan were analysed for PCB residues (Wickizer et al., 1981). All of the samples collected from 68 of the state’s 83 counties contained measurable PCB residues, ranging from trace quantities to 5.1 p.p.m. (fat basis). The mean level was 1.496 p.p.m.; 17.4% had 2–3 p.p.m.; 6.14%, more than 3 p.p.m. It was estimated that an infant breast fed for 8 months by a woman with this average PCB milk level (1.496 p.p.m.) would have a cumulated body burden of approximately 0.89 mg/kg (p.p.m.) of PCBs. Nearly one-half of these sampled women had breast milk PCB concentrations equal to or above the present FDA tolerance limit (1.5 p.p.m./fat basis) for cow’s milk. Blood PCB levels in infants ingesting PCB-contaminated breast milk may exceed those of their non-occupationally exposed mothers by as much as six-fold (Kuwabara et al., 1979). The possible effects of this chemical contamination on the growth and development of infants are at present unknown.

Because of their chemical stability and resistance to biological decomposition, polychlorinated biphenyls have become ubiquitous environmental contaminants. It is estimated that more than 1.4 billion pounds have been manufactured and introduced into the marketplace since 1929, and that 750 million pounds are still in service and available to impact the environment (Sheffy, 1979). The high lipid solubility of PCBs facilitates their entry and progressive accumulation in the food chain leading to man, with the suckling human infant at the apex. Unfortunately, little toxicological information is available on which to base hazard evaluation. Of particular concern relating to possible prenatal exposure is Barr’s recent report that PCBs enter the fetal brain compartment, though they do not seem to cross the adult blood–brain barrier (Barr, 1981).

Though these observations are reason for serious concern, the recommendation by the Wisconsin State Department of Health, in a letter to all Wisconsin physicians, stating that certain subsets of women should have their milk analysed for PCBs and insecticides, and that the Department of Health cannot recommend continuation of breast feeding if milk PCB levels in a mother are above the FDA tolerance limit, would seem premature and imprudent according to Kendrick (1980). A retrospective EPA study of the 1975–6 human milk survey and two prospective studies in progress in Wisconsin and in North Carolina may provide data which will aid in evaluating whether adverse health effects can be ascertained in human infants whose mother’s milk has higher than average levels of PCBs.

7 METHYLMERCURY POISONING IN BREAST-FED INFANTS

That human infants can be severely damaged by ingestion of a mercury fungicide solely through dietary intake of exposed mothers has been demonstrated during the recent large outbreak of methylmercury poisoning in Iraq (Amin-Zaki et al., 1976, 1980). The Iraqi outbreak of acute methylmercury poisoning from ingestion of bread made from seed wheat treated with a methylmercury fungicide
provided an opportunity to measure methylmercury intake via suckling in infants born just prior to the time when their mothers began eating contaminated bread. As shown by the example in Figure 10, suckled infants' blood mercury concentrations were frequently raised to levels greater than those of their mothers by transfer of methylmercury in milk. A number of these infants were later observed to have suffered significant adverse neurological effects. (Amin-Zaki et al., 1980).

Potentially large acute doses of chemical agents can also be transmitted from mother to suckled offspring. As much as 27% of a tracer dose of radioactive iodine administered to a lactating woman has been observed to cross the plasma–milk barrier (Nurnberger and Lipscomb, 1952). Recently, studies of mice in our laboratory have also shown that approximately 25% of an intravenous maternal dose of lead is transferred to the litter by suckling within four days, accounting for a significant fraction of the total lead excreted by the lactating mothers (Figure 11) (Keller and Doherty, 1980).
8 CONCLUSIONS

Potential teratological and toxic effects of chemical agents on the developing mammal can best be evaluated within the context of the rather extensive background of observed embryofetal and perinatal wastage, and postnatal developmental morbidity. Unfortunately, at present, our very limited knowledge of genetic and environmental factors affecting mammalian development precludes other than an empirical approach for evaluating adverse effects of environmental agents. Some general principles of development relating to embryological generation of functional units, regenerative capacities of determinate and indeterminate organ systems, and the concept of changes in reserve adaptive capacity throughout the life cycle are proposed as useful parameters for a conceptual framework with which to evaluate teratological and toxic effects of environmental agents on the developing mammal. The importance of examining dose–effect, dose–response relationships in terms of establishing quantitative estimates of prenatal or perinatal dose and evaluating quantitatively effects (response) and all subsequent postnatal stages in terms of adverse effects on reserve adaptive capacities of organ systems is emphasized.
9 REFERENCES


Perinatal Exposure and Teratological End-points


