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THE EFFECTS OF PRENATAL HEPTACHLOR EXPOSURE ON INFANT DEVELOPMENT

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THE EFFECTS OF PRENATAL HEPTACHLOR EXPOSURE ON INFANT DEVELOPMENT

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ABSTRACT

The contamination of the milk supply of the Island of Oahu, Hawaii with the pesticide heptachlor resulted in the the prenatal exposure of infants whose mothers consumed milk and milk products during the period of contamination. Heptachlor is a neurotoxic, lipophilic, organochlorine pesticide which is extremely persistent in the environment and which bioaccumulates as it progresses up the food chain. Heptachlor is known to pass the placenta and its major route of excretion is through lactation resulting in postnatal exposure of breastfed infants. While heptachlor is a known carcinogen its teratogenic effects were unknown.

A group of 120 infants participated in this study to determine if prenatal and lactational exposure to this pesticide affected physical and behavioral development. Results were analyzed in the context of a multivariate model encompassing a matrix of exposure variables and a matrix of outcome variables. Major exposure variables of concern were duration and timing of exposure, reflected by month of birth and duration of breastfeeding, and level of exposure to heptachlor, reflected by prenatal maternal milk ccnsumption and amount of heptachlor in breast milk samples. Three categories of outcome variables were assessed: physical and health measures, both perinatal and postnatal, and performance on behavioral tests at 4,8 and 12 months of age.

These criterion measures reflected the three non-lethal results of exposure to a teratogen: morphological anomalies, growth retardation and functional anomalies.

Perinatal outcome was found to be associated with maternal body levels of heptachlor. For infants who were exposed through their entire gestation, both maternal heptachlor consumption and maternal body levels of heptachlor were found to be related to certain perinatal variables, i.e., birthweight, head circumference, presence of jaundice. No effects on postnatal growth were seen. Scores on the Bayley Infant Scales at 4 and 8 months were related to duration of prenatal exposure to heptachlor. Lack of relationship to exposure at 12 months and analysis of Kohen-Raz scale scores suggested that effects seemed to consist of temporary slowing of development at early ages. These results indicate that low-level exposures to environmental contaminants may place the optimal development of infants at risk.

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INTRODUCTION

Until recently, it was thought that the unborn child was protected from adverse environmental influences by the nature of its prenatal environment. The placenta was believed to function as a barrier to drugs, chemicals and maternal disease. Furthermore, the intrauterine environment was presumed to be safe from the effects of conditions such as malnutrition or agents like radiation.

Recognition of the prenatal vulnerability of the human resulted only after McBride (1961) and Lenz (1961) pointed out the relationship between prenatal use of thalidomide by the mother and deformity of the infant. Prior to this, the biomedical community did not appreciate that the developing human was not fully protected in the intrauterine environment (Wilson, 1977a). Goldstein and Murphy (1929) had reported thirty years previously that women gave birth to deformed infants after pelvic irradiation. In the 40's Gregg (1941) found that first trimester rubella infection in the mother frequently resulted in birth defects and Warkany and his colleagues (Warkany & Nelson, 1940; Warkany & Ross, 1948) demonstrated that the development of higher animals could be altered by prenatal influences. Nonetheless, according to Wilson (1977a) it was still believed that radiation and maternal disease were exceptions to the general principle of placental functioning. As a

consequence of the thalidomide tragedy, it became recognized that not only radiation and disease, but also drugs and chemicals could adversely effect prenatal development (Spyker, 1975; Wilson, 1973, 1977a).

Teratology is the study of birth defects, or as Wilson (1973) defined it, "the study of the adverse effects of environment on developing systems" (p.4). Teratology literally means the study of monsters and teratogen, maker of monsters. Originally, the consequences of prenatal exposure to a teratogen were considered to be death, morphological defect or growth retardation (Wilson, 1977a). While it had long been noted that infants born to mothers who used alcohol or opiates heavily had behavioral disturbances, it was not until the pioneering research of Werboff and his associates (Werboff, Gottlieb, Havlena, & Word, 1961) that behavior anomalies began to be considered as teratologic outcomes (Hutchings, 1978). With this inclusion, a new field of research developed, behavioral teratology,which defined as its subject matter those behavior abnormalities which result from prenatal exposure to environmental agents (Hutchings, 1978).

Today, behavioral effects of prenatal drug or chemical exposures are well documented (Buckalew, Ross & Lewis, 1979; Coyle, Wayner & Singer, 1976; Golub & Golub, 1981; Kolata, 1978; Leonard, 1982, 1983; Spyker, 1975). Behavioral effects have been found in humans with prenatal exposure to

a wide variety of agents: alcohol (Landesman-Dwyer, Keller & Streissguth, 1978, Landesman-Dwyer, Ragozin & Little, 1981); anesthetics (Brackbill, 1976, 1979); narcotics (Wilson, Desmond & Vernaud, 1973); lead (Needleman, 1980; Needleman, Leviton & Bellinger, 1982; Shaheen, 1984); methylmercury (Clarkson et al., 1981) and polychlorinated biphenyls (PCB's) (Fein, Jacobson, Schwartz & Jacobson, in press; Jacobson, Jacobson, Fein, Schwartz & Dowler, 1984). The human literature is supplemented by a growing body of animal research (see Golub & Golub, 1981; Leonard, 1983).

Principles of Teratology

As the field developed a set of teratological principles evolved. Originally, this set of principles was delineated in reference to non-behavioral outcomes. However, there is now agreement that these principles apply to functional defects as well (Coyle, et al., 1976; Hutchings, 1978; Spyker, 1975; Wilson, 1973, 1977;).

1. There is a range of possible teratogenic outcomes: embryo or fetal death, morphological defect, growth retardation or functional deficit (Miller, 1983; Smithells, 1983; Tuchmann-Duplessis; Wilson, 1973,1977a).

While both structural and functional anomalies may occur together (e.g. Minamata disease or fetal alcohol syndrome), behavioral disfunction may occur independently of structural defect (Barlow & Sullivan, 1975; Coyle, et al., 1976; Hutchings, 1978; Rodier, 1978; Spyker, 1975, 1975a;).

Kolata (1978) noted that it has been easier to detect behavioral abnormalities in combination with physical defects since the visible anomalies tag the child. Behavioral anomalies occurring without accompanying physical defects may go unnoticed or may be attributed to some other cause. For example, Rall (cited by Weiss, 1983) questioned whether thalidomide's effects would have been discovered had they been limited to a lowering of intellectual potential.

Tuchmann-Duplessis (1983) suggested that effects of environmental agents with minimal teratogenic potency may be masked by the normal rate of occurrence of defects. It is for this reason that Kolata (1978) and Kurzel and Cetrulo (1981) noted that behavioral teratogens identified thus far have been either found in populations with a known exposure or were accompanied by structural anomalies.

Wilson (1977) proposed that while the separate sequelae of exposure to a teratogen may seem to be discrete results, in some cases the outcomes may, in fact, be related. That is, certain structural malformations or functional abnormalities may be incompatible with survival or growth retardation may be severe enough to preclude viability. Likewise, functional deficits could be due to structural deviance or growth retardation.

2. The effect of a toxic agent will vary with the developmental stage of the organism at exposure (Hayes, 1975; Wilson, 1973, 1977a).

It is axiomatic in both biology and psychology that

immature organisms are most susceptible to insult. Beyond the general vulnerability which exists during development, it has long been recognized that there are critical periods of rapid development where insult (i.e., exposure to a teratogen) will have maximal impact.

Traditionally, teratologists have focused on the period of organogenesis (the first trimester in humans) when organs are developing most rapidly. Individual organs are believed to have specific periods of vulnerability beginning with chemical differentiation and ending with completion of organogenesis (Hayes, 1975). However, with the recognition of growth retardation and functional deficits as teratologic outcomes has come the realization that histogenesis and maturation of function are also periods of vulnerability (Hayes, 1975; Lowe, 1974; Wilson, 1977a).

Extension of the time frame of vulnerability beyond the first trimester is also supported by recent research on brain development which indicates that the brain growth spurt does not begin until the second trimester (Barlow & Sullivan, 1975; Hutchings, 1978; Langman, Webster & Rodier, 1975; Leonard, 1982; Spyker, 1975a; Tuchmann-Duplessis, 1983; Weiss & Spyker, 1974). Furthermore, it is now acknowledged that birth does not constitute a boundary for susceptibility to teratogens (O'Mahony, 1982; Tuchmann-Duplessis, 1983; Spyker, 1975a; Wilson, 1977a). This is not only because brain growth and development

continue (Dobbing, 1972, 1974; Hutchings, 1978; Spyker, 1975a; Tuchmann-Duplessis, 1983; Wilson, 1977a), but also because the neonate may continue to be exposed to environmental agents through its mother's breast milk (Buckalew et al., 1979; Coyle et al., 1976; Kurzel & Cetrulo, 1981; Lowe, 1974; Weiss, 1983; Weiss & Spyker, 1974; Wilson et al., 1980).

3. As dosage increases, the frequency and degree of deviant outcomes will also increase (Wilson, 1973, 1977a).

This principle relates directly to the safety of a specific agent. That is, does a dosage exist below which there are no adverse effects, a no-observable-effects level, or is the effect limited to a decrease in the frequency of adverse outcomes with lower dosage? Generally, different thresholds exist for different manifestations, with a no-effects level being found when sufficiently small dosages are employed. Very little information exists about no-observable-effect levels for functional deficits since there is a dearth of relevant research (Timbrell, 1982; Wilson, 1973, 1977a). Furthermore, detection of a no-observable-effects level is affected by the behavior chosen as the dependent variable or criterion behavior (Barr, Keller, Rogan & Kline, 1979; Fein et al., 1983; Kolata, 1978). Failure to find a threshold for effects may be due to some extent to insensitivity of the criterion behavior.

There is general agreement, however, that behavior is a more sensitive index of teratogenicity than physical defect (Coyle et al., 1976; Mello, 1975; Rodier, 1978; Spyker, 1975, 1975a; Weiss & Spyker, 1974). While high doses may be embryolethal or cause structural change, low doses may affect behavior (Coyle et al., 1976; Hutchings, 1978; Kolata, 1978; Miller, 1983; Wilson, 1973, 1977a). For this reason Coyle et al. (1976) and Hutchings (1978) suggested that when testing drugs for functional teratogenicity, doses just below that level which is known to cause physiological malformation also should be tested (i.e., the subteratogenic level). The implication is that doses below the teratogenic level of a drug for morphological malformations may still produce behavioral abnormalities.

Included in the issue of dosage is the period of time over which the exposure occurs. Of increasing concern are long term (either chronic or subchronic) exposures to environmental agents. There is agreement that long-term, low-level exposure may be of greater import to the health and well-being of the general population than is an acute exposure which is recognized and rectified more rapidly (Burt, 1975; Fein et al., 1983; Weiss, 1983; Weiss & Spyker, 1974). This is especially true, not only because the breadth of the exposure may be greater and the exposure harder to detect and, therefore, longer lasting, but also because effects of the exposure may be subtle but important.

Furthermore, the pharmacokinetics of a low dosage, long-term exposure may be different from that of a single, higher level dose. One possible result is that at low doses, the body is able to detoxify and eliminate the chemical (Chan, O'Hara & Hayes, 1982; Fraser, 1977). However, when bioactivation occurs, i.e., when metabolism alters a compound to a more active or toxic form (Juchau, 1981), the organism must then cope with the resultant levels of the toxic agent. In such situations, Juchau (1981) speculated that bioactivation plays some sort of role in teratogenesis. Nonetheless, he noted that there is little research on this topic. On the other hand, some environmental agents bioaccumulate in adipose tissue. This may allow the chemical to reach toxic levels after a period of time or may constitute a life-long body burden of the agent (Chan et al., 1982; Jacobson et al., 1984; Leonard, 1982, 1983; Mello, 1975). Bioaccumulation is especially a concern in relation to lipophilic chemicals (Rogan, 1982) which also readily cross the placenta and consequently, tend to accumulate in the fetus and which also will be excreted by the mother in breast milk.

It should be noted that dosage, duration and timing of exposure may interact in determination of teratologic outcome (Hayes, 1975; Hutchings, 1978; Wilson, 1973, 1977a). For example, smaller doses during periods of greater sensitivity will have maximal effects. It is also agreed

that long term exposure at low dosages will produce different effects than a single large dose. The direction of effects, however, is not constant. For some agents chronic or subchronic exposure is less teratogenic since the fetus or the mother can more efficiently detoxify the agent (Chan et al., 1982). Other agents, however, which accumulate in the fetus or whose products of metabolism are more toxic than the original chemical may prove to be more harmful with longer term exposures (Chan et al., 1982; Hayes, 1975; Hutchings, 1978).

4. Susceptibility to a specific teratogen depends on the genotype of the developing organism and its interaction with a specific environment (Wilson, 1973,1977a).

Stated more simply, there is individual susceptibility to effects of an agent. That is, some individuals will be affected at very low doses, while others would require exposure to higher levels of a teratogen for adverse effects to be expressed (Chan et al., 1982).

In animal research this principle is readily demonstrated, with species as well as intra-and inter-litter differences in deviant development after exposure. An example which had tragic implications is thalidomide which showed no teratogenic effects in the species on which it was originally tested, but which was later found to be a potent teratogen in primates and humans (Mellin & Katzenstein, 1962a, 1962b; Wilson, 1973). While teratologic research involving humans is not possible in most instances, the

substitution of animal research may not be completely satisfactory because of inter-species differences in susceptibility to a specific teratogen (Kurzel & Cetrulo, 1981).

Also relevant in regard to individual susceptibility may be sex of the organism. Plaa (1982) indicated that adverse outcome may be sex-related, either due to sex hormone effects on pharmacokinetics or sex related differences in organ susceptibility. For example, reversals in sex-ratio of male to female births have occasionally been a clue to the presence of a harmful agent as in the Love Canal incident (Burch, 1984).

Maternal genotype may also be a factor in individual susceptibility since it determines some aspects of the intrauterine environment, e.g., maternal physiology, differences in ability to detoxify an agent, differences in storage of an agent (Tuchmann-Duplessis, 1983). As a result teratological outcome should always be considered a result of the complex interaction of genotype of the embryo, maternal genotype and environmental factors.

Dorfman (1974) stated that specific genetic sensitivity might be especially important at the present time in light of the rapidly changing nature of the environment. Since humans are being exposed to chemicals not encountered in the past, there are now new factors in evolutionary selection as a result of alteration of the environment.

Fein, Schwartz, Jacobson and Jacobson (1983) argued that individual susceptibility to toxic effects is a major reason to abandon the disease model when studying exposures to potentially harmful environmental agents. They instead advocated a multiple effects model in which prenatal exposure does not inevitably lead to a specific set of consequences as a disease model would predict, but instead, may lead to one of a number of eventualities including behavioral signs depending on individual susceptibility to the specific agent as well as timing of exposure, length of exposure, remediating factors in the environment, etc. Wilson (1973) made a similar point. He wrote, "The probability of multifactorial causation, whether involving interaction of genetic loci and adverse factors in the environment, or multiple factors within either category, should not be lightly regarded..." (p.15).

5. Specific agents act in specific ways (called mechanisms) to cause pathogenesis.

Generally, this is taken to mean that characteristic patterns of defects tend to appear after exposure to a particular teratogenic agent. While it has been found that expression of outcomes may vary with exposure to the same agent and that similar defects may be found after exposure to different agents (Wilson, 1973, 1977a), nevertheless, it is hypothesized that whatever effects are seen result from one of nine mechanisms. Mechanisms, in this context, are

defined as "early, presumably determining, reactions of developing cells to extraneous influences" (Wilson, 1973, p.23). The nine mechanisms involved in teratogenesis are: mutation, chromosomal nondisjunction or breaks, mitotic interference, altered nucleic acid integrity or function, lack of normal precursors or substrates, altered energy sources, changed membrane characteristics, osmolar imbalance, and enzyme inhibition or induction (Wilson, 1973,1977a). It is believed that one agent can initiate one or more of the mechanisms and that the mechanisms can be initiated by different agents.

Wilson (1977) noted that since these changes are at the molecular or subcellular level, they cannot be detected until observable pathological changes develop. At this stage in the development of the field the specific mechanisms initiated by a certain agent are for the most part unknown (Kimbrough, 1982; Kurzel & Cetrulo, 1981; Van Gelder, 1972). Wilson (1977) wrote, "Since relatively little is presently known about the earliest reactions to most teratogenic causes, the designation of any as being more significant than others is largely empirical(p.54)." Since the agent can have a direct effect on the embryo, fetus or neonate or may act indirectly by altering maternal or placental functioning (Waddell & Marlowe, 1981), detection of the site and mechanism of teratogenesis is difficult. Genetic susceptibility also contributes to the

arduousness of the task as does the fact that expression of effect will vary dependent on timing, duration and dosage of exposure.

The difficulty of such research is illustrated by the fact that the mechanisms of action of thalidomide, one of the most thoroughly studied teratogens, are still unknown (Timbrell, 1982). This state of ignorance exists in relation to structural as well as functional defects. However, research on teratogenicity of specific agents continues, with research on mechanisms of action being subsequent to demonstration of effect.

Since teratology as a science is itself in its infancy the necessity for further research is obvious. Moreover, because of the changing nature of the environment, humans are increasingly being exposed to potential hazards about which no information exists (Tuchmann-Duplessis, 1983). Kotin (1974) suggested that the proliferating industrialization of society has resulted in a change in the nature of risks: hazards are now primarily chemical rather than biological; the implications of the increasing use of synthetic agents are largely unknown; and multiple sources of insult are more frequent. Furthermore, advances in modern medicine and pharmaceutics carry with them unknown hazards to reproduction, reproductive outcome, and postnatal development, both physical and behavioral. Multiple drug use during pregnancy is common (Hill, 1973; Hill, Craig,

Chaney, Tennyson & McCulley, 1977; Stewart, Cluff & Philp, 1977). Deliberate exposure through ingestion of drugs or consumption of foods containing additives presents a potential hazard as do other types of exposures: occupational, either directly or indirectly through contamination of the home; accidental exposures through a specific contamination such as the grain incident in Iraq or PBB in Michigan; and ambient exposure occurring through contaminated air, water or food (Barr, Keller, Rogan & Kline, 1979).

Research on Behavioral Teratogens: Justifications and Impediments

Concommitant with increased exposures to potential teratogens is an increased need for knowledge about teratogens, especially those with functional effects. Rodier (1978) proposed, "The medical, social and psychological impact of a teratogen lethal to embryos or fetuses is minor compared to the sequelae of a nonlethal teratogen (p.397)". That is, while a lethal teratogen produces a tragic result, non-lethal teratogens have major, life-long implications for the child, parents and society. Kolata (1978) submitted that the covert teratologic outcome of behavioral or intellectual impairment may be as disturbing as physical deformity. With behavioral and morphological defects equally undesirable and with those

factors leading to functional defects increasing (Allen, Hargraves, Hsia & Lin, 1979; Kimbrough, 1982), it becomes imperative to include research on behavioral teratogenesis as part of the evaluation of drugs and environmental agents (Kurzel & Cetrulo, 1981). While testing of agents for behavioral teratogenicity is mandated by France, Japan and the United Kingdom, it is not currently required in the United States. Manson, Zenick and Costlow (1982) predicted that such testing will eventually be required by the FDA and the EPA. Nonetheless, there may be aspects of and agents already in the environment which impact on behavioral development.

A number of reasons exist to justify research on behavioral teratogens. Of major importance is the fact that behavior is believed to be a more sensitive indicator than structure of teratologic action (Coyle et al., 1976). That is, behavior disfunction or change may be the earliest indication of toxicity (Michael, 1982; Spyker, 1975; Weiss, 1983), earliest being taken to mean either the first manifestation of the toxic process or at a lower dosage than other disadvantageous outcomes.

A second major justification for behavioral research is that behavior represents the endpoint in the functional integration of the CNS (Manson et al., 1982; Weiss, 1983). Mello (1975) argued that behavior may reveal defects that may not be detectable through physiological or histological

analysis. Barr et al. (1979), in summarizing a workshop on perinatal and postnatal defects arising from chemical exposures, expressed the opinion that functional defects may actually comprise the largest category of outcomes of injurious chemical exposures, again because behavior reflects the complex interaction of many systems. For this reason Manson et al. (1982) as well as Weiss (1983) observed that behavior functions as an assay system reflecting total functional capacity of the organism. That is, whether the agent 1) works directly on the CNS because of the incomplete blood-brain barrier (Brackbill, 1979), 2) affects neurotransmitters (see Barlow & Sullivan, 1975; Leonard,1982), 3) alters structure, or 4) modifies the biochemistry of the organism, the deviation will be reflected in function.

The principle of genetic susceptibility is related to a third reason why behavioral research is important. Susceptibility to a specific agent has been conceived of as normally distributed with most individuals only somewhat susceptible to teratologic damage, a few invulnerable to effect, and a few extremely susceptible (Fein et al., 1983; Fraser, 1977a). Consequently, an agent which might lead to subtle dysfunction in some individuals, may produce major impairment in others, i.e., those at the high end of the distribution of susceptibility. Conversely, clinically detectable effects in the most susceptible may signal more

subtle impairment in those less suceptible. In either case, however, behavioral research plays a most important role. Indeed, even the Clean Air Act of 1976 mandates the EPA to consider the most susceptible subgroup when setting standards (Omenn, 1982).

Equally important is the possibility that behavior changes in the infant or child (or even in the infant animal) may have secondary consequences (Fein et al., 1983; Leonard, 1983). Since the child exists in an environmental matrix, any abnormalities in its behavior will lead to differences in the way it is perceived and treated. For example, infants exposed prenatally to low levels of PCB have been found to be more autonomically immature and to be less responsive (Jacobson et al., 1984) and therefore, present a different stimulus complex for their parents. When as a result of exposure to some agent, the child is clumsy or irritable or hyperactive, the parent must then deal with a child who differs from the norm. Not only is the behavior itself modified, but also the reaction of the environment to the child. The recognition of this effect in animals is one on the reasons why cross-fostering is suggested in animal studies (Joffe, 1969; Leonard, 1983). Not only is the affected behavior important in itself (Spyker, 1975), but the environmental consequences of altered behavior must also be considered in determining the effects of a prenatal exposure.

Finally, behavior is an important indication of teratologic effect since its evaluation is non-destructive to the organism (Weiss, 1983) and does not require physically invasive techniques which may disrupt normal function (Burt, 1975). In fact, Dews (1975) defines behavioral toxicology (the parent field of behavioral teratology) as "...the science dealing with the effects of nontherapeutic, nonphysiological chemicals on the behavior of more or less intact subjects" (p.439). This may be especially significant when studying a human exposure where potential harm to the subject may not appear sufficient to justify more invasive testing.

Despite the importance of testing for behavioral birth defects, there are many difficulties inherent in such research. A major problem is that, with the exception of accidental exposures, there is no ethical way to test for such effects in humans (Fraser, 1977; Kurzel & Cetrulo, 1981). Teratologists are necessarily restricted to retrospective studies or research with animals. In the later case the issue of extrapolation of results to humans must be addressed. Unfortunately, however, it is precisely in this area of toxicology that extrapolation to humans is most difficult (Hogan & Hoel, 1982). There are two major reasons for this: first, relatively little is known about the mechanisms underlying teratogenesis; second, species differ in terms of anatomy, biochemistry, physiological

functioning, and pharmacokinetics, as well as in the timing of developmental events (Hogan & Hoel, 1982). It is commonly acknowledged that no one species of animals can serve as an adequate model for human effects (Fraser, 1977a; Norton, 1982). This is especially true in relation to behavioral teratogenesis (Fraser, 1977a; Kolata, 1978) particularly due to the much greater encephalization in humans (O'Mahony, 1982) and since behaviors in humans and animals may not be strictly analogous (Barlow & Sullivan, 1975; Golub & Golub, 1981; Hutchings, 1978; Rodier, 1978). An additional consideration raised by Buckalew (1978) and Buckalew et al. (1979) is that animals surviving exposure to a teratogen may be genetically protected (i.e., less susceptible) and may yield results only applicable to such protected organisms. Strobino, Kline and Stein (1978) suggested that conceptions that survive may be but a small percentage of all anomalous conceptions. Regardless of these problems, animal research is the only alternative in most instances. Positive results from non-human research can only be suggestive of effects in humans. Unfortunately, negative results from non-human research do not allow inference of no effect in humans (Interagency Regulatory Liaison Group, 1979).

An additional problem in teratological research is that interactions occur which affect the expression of disadvantageous result. One such interaction has been discussed previously, that of teratogen with genotype. A

second type of interaction which has been found is between teratogen and maternal variables such as nutrition (Mahaffey & Vanderveen, 1979; Weatherholtz, Campbell & Webb, 1969). Teratogens have also been demonstrated to interact with pharmacological agents (Fraser, 1977). It is hypothesized that this effect may be due to the environmental agent's altering of microsomal enzyme function either through induction or inhibition (Conney & Burns, 1972; Street, 1969; Timbrell, 1982). An example of such an interaction is seen in the modified steriod metabolism of animals exposed to chlorinated hydrocarbons (Bulger & Kupfer, 1983; Conney & Burns, 1972) and in the increased toxicity of heptachlor in infant rats pretreated with phenobarbital (Harbison, 1975). A fourth type of interaction is between teratogen and bacterial or viral infection (Crocker et al., 1976; Lowe, 1974).

These various types of interactions make interpretation of results difficult especially when dose is so low that the agent escapes suspicion (Wilson, 1973). However, it is becoming clear that in all situations except those involving extremely high doses or very potent, teratogens where all will be affected that teratologic outcome is multiply determined. A multiple effects model is considered the only feasible explanatory model (Fein et al., 1983; Fraser, 1977; Weiss, 1983). Even the principles of teratology outlined earlier imply multiple determination of effects; i.e.,

teratologic effect depends on timing, dosage, agent and individual genotype. In many instances, given the same dose or exposure to a specific agent, individuals will show different effects depending on individual susceptibility or the presence of predisposing conditions. Where dose levels are high or the teratogen is highly potent a characteristic pattern of effects may be seen as a clinical sign of exposure, but that when exposure is low-level effects are less likely to be specific to a particular agent (Fein et al., 1983; Smithells, 1983) and are very likely to be vague, subjective and not easily quantifiable (Mello, 1975). Consequently, it has been proposed that a multiple effects model be used rather than the more traditional disease model which implies a dose-response relationship and a characteristic set of symptoms of exposure.

In research on low doses of toxins, a number of possible effects, often very subtle, must be explored bearing in mind that only the most susceptible will be affected. Research, however, is difficult since some defects may be masked either because of their subtlety or by the natural occurrence rates of behavioral anomalies (Leonard, 1983; Tuchmann-Duplessis, 1983; Weiss & Spyker, 1974). Fraser (1977a) suggested that when the dose response curve merges with the tail of the natural distribution of anomalies, the effects of the teratogen may be masked by the background noise. However, it should be remembered that

even a small shift in a normal distribution or an increase in the variability has an effect on the tails of the distribution (Fein et al., 1983; Fraser, 1977a; Needleman et al., 1982). While the shift in the mean of the distribution may be small (and be in itself of no clinical importance), the increased frequency of the anomaly may have significant implications. This has been illustrated by the findings of Needleman et al. (1982) in regard to the relationship of higher lead exposure in children to IQ where children with high lead levels were less likely to have IQs above 125 and were more likely to have IQs below 80 although the IQ differential between the high-lead and low-lead children was less than 5 points.

While some conditions may interact with a teratogen to exacerbate disadvantageous outcome, it is also true that other variables may work to protect against deleterious effects. The obverse of a continuum of susceptibility is a continuum of prophelaxis. Because of the youth of the science of teratology, little is known about those factors which increase susceptibility, but almost nothing is known about variables which provide protection for the organism (Cohen, Sigman, Parmelee, & Beckwith, in press). In relation to functional defects, Sameroff and Chandler's (1975) concept of a continuum of caretaking casualty may be most germane. With exposure to a teratogen viewed as a reproductive risk, outcome may depend on the environment in

which the infant and young child exists. A superior environment may mitigate deleterious effects, while a defective environment may exacerbate them. This complex organism-environment interaction contributes to the difficulty of detecting subtle behavioral effects but clearly demonstrates why a dose-response disease model is not tenable.

A further complication encountered in research on behavioral teratogens is the inaccuracy in prediction of future functioning. This lack of predictiveness is due to a number of factors. The first is what Sameroff and Chandler (1975) call the self-righting tendency, that is, there seems to be a directionality in development which presses toward normality despite adverse circumstances (See Honzik, 1976; Scarr-Salapatek, 1976; McCall,1979). A second factor which decreases the accuracy of prediction is that an infant or child's behavior is not strictly an immature representation of mature functioning. There is general consensus in psychology that development is not linear, i.e., nervous system functioning (Prechtl, 1981), motor behavior (Connolly, 1981), cognitive functioning (Piaget, 1952), as well as those behaviors defined as comprising intelligence (McCall, 1979) are qualitatively different in maturing organisms. Acceptance of this process leads to the conclusion that prediction from early functioning will be imperfect. If, in addition, the strong influence of

environment on development (Kopp & Krakow, 1983) and the self-righting tendency discussed above are acknowledged, then the only conclusion that can be reached is that accurate prediction can only be made when multiple factors are taken into account. This conclusion is supported by most of the literature on children at risk (see Cohen & Parmelee, 1983; Kopp & Krakow, 1983; Kopp & Parmelee, 1979; Sameroff, 1981; Werner & Smith, 1982).

The issue of prediction of future functioning is related to another issue in teratology: that of latent effects. While present functioning may appear to be unaffected, a lesson that DES (diethylstilbestral) has taught is that latent effects of prenatal exposure are possible (Leonard, 1983). To illustrate, while it has long been recognized that prenatal exposure to radiation is teratogenic, research is now beginning to suggest that prenatal exposure to low levels of radiation may be associated with an increased risk of developing cancer as well as reduction in growth and development (Boice, 1982). The possibility of such latent effects necessitates the use of a longitudinal research design in order to assess whether teratologic effects will emerge during postnatal development (Fein et al., 1983; Miller, 1983; Spyker, 1975, 1975a; Tuchmann-Duplessis, 1983; Weiss and Spyker, 1974). Such delayed effects could be expressed as functional deficit or behavioral disorder, but as Strobino et al. (1978) noted,

there is no specific method for anticipating future latent effects.

The possibility of latent behavioral effects is especially important in relation to prenatal exposure. The initial behavioral repertoire of infants is limited. In humans it is possible that defects might not be manifested (or detected) until language development occurs or until the child begins school (Fein et al., 1983). In other cases it has been proposed that the affected individual could develop compensatory mechanisms which would mask the deficit until aging or stress overloaded the system (Spyker, 1975).

Latent behavioral deficits have been observed to result from early or prenatal exposure to environmental contaminants. Spyker (1975) found that mice prenatally exposed to methymercury could not be distinguished from non-treated mice at birth; but with age, behavioral deficits developed. The early subtle deficits proved to be precursors of more severe problems such as motor impairment, generalized debilitation, neuropathology and early aging. Similarly, long term functional anomalies have been observed in humans after exposure to methylmercury (Weiss & Clarkson, 1982), lead (Needleman, 1982) and PCBs (Harada, 1976). Furthermore, prenatally exposed individuals would be more likely to exhibit latent effects simply due to their life expectancy. Since they would be expected to survive upwards of 70 years, long-term effects would have increased

opportunity for expression (Garfunkel, 1982; Omenn, 1982). Therefore, absence of detectable anomaly at birth does not negate possibility of later emergence of effect.

Contamination of the Milk Supply of Hawaii

When accidental exposures of a population to teratogens occur there is an urgent need for information on the potential effects. If no animal literature exists upon which to base predictions, it then becomes imperative to study the exposed population in order to detect what consequences, if any, resulted from the exposure.

Such a situation, unfortunately occurred in Hawaii when it was discovered that the milk supply of the island of Oahu was contaminated with the organochlorine pesticide heptachlor at levels exceeding the Food and Drug Administration's (FDA) allowable level of .3 ppm on a lipid basis through consumption by dairy cows of contaminated feed. (In this presentation the term heptachlor will always refer to heptachlor epoxide since the epoxide is formed so readily that detection of heptachlor in its non-metabolized form is rare.) Public announcement of the contamination and withdrawal of a number of milk products occurred on March 18, 1982 with 11 subsequent recalls of milk products during the next several months. Initial estimate of the contamination period was from January, 1982 when the contamination was first detected until March, 1982 when the

public announcement and product withdrawal was made. However, subsequent testing of stored milk samples revealed a contamination period of from 12 to 19 months duration (Hylin, 1982; Pfenninger et al., 1984; Smith, 1982b). Testing of commercial milk samples in January, 1982 revealed levels far in excess of the FDA's acceptable limits, and in the case of several samples, in excess of the no-effect level (Cayetano, 1983; Hylin, 1982; Johnson, 1982; Smith, 1982). Since importation of fresh milk into Hawaii was prohibited at that time, it can be assumed that all of Oahu's fresh-milk-consuming population (and breast-fed infants whose mothers consumed fresh milk) were exposed for a relatively long period of time to levels of heptachlor in excess of federal limits.

While the FDA set a zero tolerance for heptachlor in food, the action level (that level at which the product must be withdrawn from the market) was set at the limit of detection at that time, .3 ppm (Smith, 1982). In order to increase the margin of safety for consumers to an acceptable level the Environmental Protection Agency (EPA) recommended in September, 1982 that the FDA lower the action level for heptachlor in milk to .1 ppm (Johnson, 1982). Modern instruments are more sensitive and able to detect lower levels of heptachlor; however, at the present time economic costs to producers of meeting action levels are an

additional factor considered in setting federal action levels (Johnson, 1982; Smith, 1982).

As noted, contamination of the milk supply occurred through contamination of cattle feed. Although heptachlor's registration was withdrawn in 1978, certain uses of heptachlor were given phase-out periods, with the longest phase-out period granted to pineapple growers in Hawaii, until December 31, 1982 (Environmental Protection Agency, 1978). Heptachlor was used in Hawaii to kill ants on pineapple plants. Pineapple leaves (green chop) had been used in Hawaii as cattle feed for over 20 years. However, the EPA did not alter its action level of .03 ppm for cattle feed even though it was known that at this level heptachlor would begin to accumulate in milk and meat at levels beyond the federal action level (Cayetano, 1983). Harvesting of pineapple leaves for feed was allowed 12 months after spraying of a field. Unfortunately, heptachlor is a persistent pesticide and does not degrade significantly in this time (Smith, 1982). In addition, in the late 1970's a new machine was developed to harvest the green chop which was able to recover almost the entire plant including the lower leaves which would contain more heptachlor (Cayetano, 1983; Smith, 1982). Further factors contributing to the contamination of the milk supply were the harvesting of the plants before the requisite time period had elapsed (Smith, 1982) and failure of both the Hawaii Department of

Agriculture and the pineapple growers to monitor heptachlor use on pineapple plants (Cayetano, 1983). Subsequent testing of stored green chop samples indicated contamination of the cattle feed as early as April, 1981 (Hylin, 1982).

Testing of 75 human milk samples by the EPA Pesticide Hazard Assessment Project at the University of Hawaii soon after announcement of the bovine milk contamination revealed an average level of .14 ppm heptachlor in the samples (Johnson, 1982) which was below the acceptable level for commercially sold milk at that time. However, when the EPA calculated a worst case example of the highest 20% of the samples, a mean value of .26 ppm heptachlor was found (Johnson, 1983). A previous study of organochlorines in human breast milk conducted in Hawaii in 1979-1980 found a mean of .036 ppm heptachlor in the samples (Takahashi, Saidin, Takei & Wong, 1981). The action level for heptachlor in commercial milk was lowered in September, 1982 in order to provide an adequate margin-of-safety taking into account the duration of the exposure of the population. Nevertheless, it was noted that even the lowered level of .1 ppm on a lipid basis, would not give the standard margin-of-safety of 100 X the no-observable-effect level for infants less than seven months old (Johnson, 1982). Since the mean level of heptachlor in human milk was above the acceptable limit for commercially sold milk and since the .1 ppm limit was acknowledged to be inadequate for infants

under 7 months, the levels of heptachlor found in mothers' milk were a concern (Norton, 1982).

Because cows culled from the dairy herds were sold for ground beef, there was some contaminated meat sold in the period April, 1981 to April, 1982. However it was estimated that local beef comprised only 1.6% of the ground beef sold on Oahu and did not constitute an appreciable source of exposure (Johnson, 1982).

Toxicologic Characteristics of Heptachlor

Heptachlor is an organochlorine pesticide of the cyclodiene family known to be extremely persistent in the environment. Heptachlor tends to accumulate in foods, in animals and in humans (Allen et al., 1979). In addition, it biomagnifies or bioaccumulates as it progresses up the food chain (Hayes, 1975; Rogan, Bagniewska & Damstra, 1980) so that a 10 to 20 fold increase is found in body fat and milk relative to residues in food (Johnson, 1982). Heptachlor is metabolized to heptachlor epoxide, a more toxic form (EPA, 1980).

Heptachlor is lipophilic and is stored in fat and body organs (Cassarett, Fryer, Yauger & Klemmer, 1968; Hayes, 1975). Stored levels have been found to reflect the body burden as well as the amount of heptachlor in the diet (EPA, 1980). A three-compartment model is usually assumed, with the concentration in organs and tissue dependent on blood

flow (Ecobichon & Joy, 1982). Excretion is primarily through lactation although some urinary excretion has been found. Fecal excretion is known to occur in animals, but has not been found in humans (Hayes, 1975; EPA, 1976).

Heptachlor and heptachlor epoxide are neurotoxic in high doses (Hayes, 1975; EPA, 1980). Symptoms of poisoning are headache, nausea, vomiting, dizziness and convulsions, with convulsions usually appearing before any other signs of poisoning (Allen et al., 1979). The primary site of action of cyclodiene insecticides is the central nervous system and the mechanism of action is thought to be hyperreactiveness of the postsynaptic cell either through depression of inhibitory action or increase of excitatory input (Ecobichon & Joy, 1982). The dose at which 50 % of the litter dies (the LD50) ranges from 6 to 531 mg/kg depending on the test species and method of administration used (EPA, 1980). It has also been found that toxicity of heptachlor but not heptachlor epoxide is affected by the level of protein in the diet in rats (Webb & Miranda, 1973).

Sufficient evidence of carcinogenicity existed to justify withdrawal of registration of heptachlor by the EPA (EPA, 1978). Although Velsicol Corporation, manufacturer of heptachlor, disputes many of the findings (Velsicol Chemical Corporation, 1983), all other reviews of research on heptachlor conclude that heptachlor is carcinogenic in animals with the site of most tumors being the liver (Allen

et al., 1979; Epstein, 1976; IARC, 1979; EPA, 1976, 1980). An unpublished study of chronic low-level feedings in dogs reported liver changes after two years of exposure (cited in Johnson, 1982). Research indicates that organochlorine pesticides typically tend to cause liver cell changes and carcinomas (Hayes, 1982).

Epidemiological studies conducted on highly exposed pesticide workers did not show an increase of deaths from cancer (Wang & MacMahon, 1979a, 1979b). However, these studies were limited in both scope and duration (EPA, 1980). While Infante, Epstein and Newton (1978) have suggested a possible relationship between exposure to chlordane and heptachlor and the development of neuroblastomas, blood dyscrasias and acute aplastic anemia, no definitive evidence exists on the carcinogenicity of heptachlor in humans (IARC, 1979).

Evidence on mutagenicity is mixed. No mutagenicity was found in studies using Salmonella typhimurium and Drosophilia melanogaster (Marshall, Dorough & Swim, 1976; Shirasu, Moriya, Kato, Furuhashi & Kada, 1976). However, Cerey, Izakovic & Ruttkay-Nedecka (1973) and Markarjan (1966) found mutagenic changes after heptachlor exposure in rats and mice, respectively.

A number of reproductive effects have been found to result from exposure to heptachlor. Injection of eggs with heptachlor resulted in reduction of hatchability, but no

abnormal chicks (Smith, Weber & Reid, 1970). However, exposure of sea urchins produced abnormal embryos (Bresch & Arendt, 1977). Reduced fertility in rats, increased deaths of pups, resorbtion, and some fetal anomalies were reported by Mestitzova and Beno (1966) and Mestitzova (1967). Velsicol (1983) summarized an unpublished study by the Kettering Laboratory (1959) which found increased mortality of suckling rats when the mothers were fed a diet containing 20 ppm heptachlor. Second generation pups had a high mortality rate regardless of dose. The Kettering Lab reported that they could not continue the analysis of pup mortality because the dams were eating the pups. Nonetheless, they concluded that heptachlor had no reproductive effect. Several other unpublished studies were cited by Velsicol (1983) to support their contention that heptachlor has no reproductive effects. An unpublished study of dogs by Velsicol reports no teratologic effects of heptachlor exposure (cited in Johnson, 1982). However, these unpublished reports remain to be reviewed before final conclusions about reproductive or teratogenic effects are made in the light of the reversal of the conclusions in other research funded by Velsicol after review by independent researchers (See Cayetano, 1982; EPA, 1980).

It is well known that cyclodiene insecticides induce hepatic microsomal enzymes (Allen et al., 1979; Hayes, 1975; EPA, 1976, 1980). Microsomal enzymes biotransform endogenous

and exogenous substances, i.e., estrogen and heptachlor, respectively (Morgan, 1982). While microsomal enzymes detoxify substances, occasionally toxicity may increase after metabolism, e.g., as when heptachlor is metabolized into heptachlor epoxide.

Heptachlor and heptachlor epoxide are considered to be among the most potent and persistent microsomal enzyme inducers (DeBruin, 1976; Kinoshita & Kempf, 1970; Morgan, 1982). The no-effect dietary level for induction by heptachlor was found to be 1 ppm (Kinoshita & Kempf, 1970). Matsumura (1975) noted that the levels of organochlorines encountered in the environment are probably enough to influence the microsomal enzyme system in the human although T. Norton (personal communication, March 22, 1985) has expressed the opinion that induction occurs at levels 30-40 times environmental levels. Induction aids in metabolism of heptachlor, but prolonged induction can lead to liver changes. Hayes (1982) noted that the liver changes due to prolonged induction may lead to cancer.

Another undesirable effect of induction is that pharmacological effects of drugs may also be altered (DeBruin, 1976). In fact, the most serious consequence of induction by pesticides is considered to be the accelerated metabolism and excretion of steriod hormones (Morgan, 1982; Wilson, 1977a, 1977b). This is thought to be one explanation of reproductive failure resulting from exposures

to some pesticides (Bulger & Kupfer, 1983; Morgan, 1982). It is also hypothesized that induction of microsomal enzymes may have an effect on gestational processes by decreasing available hormones (O'Leary, Davies, Edmundson & Reich, 1970). Increased metabolism of estrogen may explain the pup killing which disrupted the Kettering (cited in Velsicol, 1983) reproductive study. Svare, Broida, Kinsley and Mann (1984) found differences in pup killing in mice when estrogen levels of the mothers were lowered. Waddell and Marlowe (1981) in noting the importance of endogenous steriods in prenatal development expressed surprise that so little research has been done on the effects of chemicals and drugs on these systems. Matsumura (1975) also called attention to the necessity of further research on these important secondary effects of exposure to organochlorines.

Heptachlor as Potential Human Teratogen

Prenatal exposure is known to occur since it has been shown that heptachlor crosses the placenta (EPA, 1980). Indeed, Reynolds (1983) wrote that by far the most important factor in whether an agent can be embryotoxic, is whether it is lipophilic, and thus can cross the placenta readily. Furthermore, for lipophilic chemicals such as heptachlor accumulation in the fetus depends on length of prenatal exposure (Reynolds, 1983). Zavon, Tye and Latorre (1969) as well as Curley, Copeland and Kimbrough (1969) reported

detection of a number of organochlorine insecticides including heptachlor epoxide in the tissues of stillborn fetuses and the tissue of infants dying in the perinatal period. Selby, Newell, Hauser and Junker (1969) found heptachlor and heptachlor epoxide in the blood of pregnant women and at concentrated levels in their placentas. Polishuk et al. (1970) detected organochlorine pesticides in maternal fat, blood and umbilical cord blood. Heptachlor epoxide has been found as well in uterine muscle and amniotic fluid, with concentrations in the following descending order: fetal blood, amniotic fluid, placenta, uterine muscle, maternal adipose tissue and maternal blood leading to the conclusion that heptachlor concentrates in the fetus (Polishuk, Wassermann, Wassermann, Cucos & Ron, 1977).

Clearly then, heptachlor and heptachlor epoxide must be considered at least as potential teratogens since prenatal exposure occurs if the mother has ingested heptachlor (EPA, 1980). Sternberg (1979) suggested that while no insecticides have yet been shown to be teratogenic in humans, insecticides at low doses may interact with other factors to the disadvantage of the developing fetus. Golub and Golub (1981) observed that teratogenesis is possible in long-term, low-level exposures to pesticides.

Postnatal exposure can also occur through nursing. In fact, the major route of excretion of organochlorine

insecticides is through lactation (Finberg, 1977; Jensen, 1983; Kurzel & Cetrulo, 1981; Rogan et al., 1980). The widespread use and the extreme persistence of such pesticides have resulted in their detection in human milk around the world (Jensen, 1983; Kroger, 1972; Savage, 1975; Wolff, 1983). The persistence of these compounds was one of their unique and major advantages in pest control, but also led to the discontinuation of their use (Savage, 1976). Their persistence in the environment also contributes to their propensity for bioaccumulation in the food chain. Rogan et al. (1980) consider nursing infants to be at the top of the food chain in relation to these lipid soluble, persistent chemicals and, as a result, exposed to higher levels than the rest of the population.

Savage (1976) in a national survey of chlorinated hydrocarbons in human breast milk reported levels of heptachlor epoxide ranging from .015 to 2.050 ppm on a fat adjusted basis. The mean level for the 1,436 samples was 0.09 ppm with the highest mean level found in the Southeastern United States. A repeat of this survey for the years 1977-1983 (Savage, in press) found the geometric mean of all samples to be .060 ppm with the Southeast again having the highest mean level, .069 ppm. The total number of milk samples included in the survey was 1842 with 1011 having levels of heptachlor epoxide above the limit of detection. The trend, then, in the United States as a whole

is a decrease in heptachlor expoxide in human milk, from .09 to .06 ppm.

In Hawaii, a survey was made of organochlorine residues in human milk in 1979-1980 (Takahashi et al., 1981). Fifty samples were analyzed yielding a mean level of heptachlor epoxide of .036 ppm on a lipid basis with a range of .001 to .067 ppm. All samples tested had detectable levels of heptachlor. It was calculated that at the highest levels a 5 kg infant would consume approximately 2.0 ug/kg of heptachlor a day, 4 times the acceptable-daily-intake of 0.5 ug/kg a day set by the World Health Organization (Pfenninger et al., 1984; WHO, 1970). A more recent survey (Pfenninger et al., 1984) undertaken to assess levels of heptachlor in human milk as a result of the commercial milk contamination found the mean level to be .122 ppm on a lipid basis. After the contamination was contained, the mean heptachlor in the milk samples returned to precontamination levels, .037 ppm, in approximately 11 months. Heptachlor levels in the human milk samples of mothers living in Hawaii during the period January-March 1982 were found to be correlated (.26, p=.01) with milk fat consumption. No significant correlation was found between heptachlor in the breast milk samples and beef consumption. In all, 426 samples were analyzed which had been collected in the time period August 1981-June 1983.

Human milk levels fell to precontamination levels

within a year of the withdrawal from the market of the affected bovine milk. However, the level of heptachlor in human milk in Hawaii did not show the overall downward trend in heptachlor levels of mainland human milk since 1976 (Savage, 1976, in press). This, however, is logically consistent with the fact that heptachlor use has been banned in the rest of the United States since 1978 while registered use continued in Hawaii until December, 1982.

In the fields of medicine and toxicology there is concern about effects of exposure through breastfeeding to environmental agents in general and organochlorine pesticides in particular. This concern centers on the conflict of the known benefits of breast feeding versus the unknown consequences of exposure to environmental agents via the breast milk (Barr, 1981; Jelliffe & Jelliffe, 1978; Rogan et al., 1980; Wolff, 1983). The benefits of breast feeding to both the infant and mother have been thoroughly discussed elsewhere (see Jelliffe & Jelliffe, 1978; Short, 1984). However, there is general consensus that the presence of environmental contaminants in human milk presents a legitimate cause for concern (Morgan, 1982). Jensen (1983) wrote that given the lack of research in this area, the possibility of injurious effects can not be dismissed. Wilson et al. (1980) labelled the presently available information in this area inadequate and noted that with the numbers of women breastfeeding increasing the

concern about the consequences of passing contaminants through the milk will also increase.

Unfortunately, knowledge of the pharmacokinetics of drugs in breast milk is scant at best. However, it is known that drugs which are lipid soluble, not easily metabolized and which are stored in the body (usually the fat) present the most threat to the infant (Wolff, 1983). A three compartment model has been proposed with storage in a deep compartment (adipose tissue) and a transfer to milk via the blood (Wilson et al., 1980; Wolff, 1983).

Factors which may influence excretion in the milk include 1) the milk-plasma ratio (M/P ratio) of concentration of the chemical, 2) polarity, and 3) lipid solubility as well as the 4) dose and 5) duration of exposure (Wilson et al., 1980). However, knowledge of the pharmacokinetics of drug excretion in human milk is far from complete.

Nonetheless, there is agreement that organochlorine insecticide residues in human milk present some risk to the nursing infant (Jensen, 1983; Matsumura, 1975; Wolff, 1983). Wilson et al. (1980) speculated that the non-existence of evidence of the deleterious effects of environmental agents in breast milk is due to failure to relate problems in the infant to exposure of the mother. They also noted that the inability to detect low levels of environmental pollutants may also be a factor. Morgan (1982) concluded that not only

is the range of effects of organochlorines in breast milk unknown, but also, at this time, it is impossible to predict what effects might occur.

Organochlorines in general exhibit a number of characteristics which make them likely to be excreted in breast milk: they are fat soluble; they are not efficiently metabolized; they are persistent in the environment; even with low environmental levels they tend to accumulate in adipose tissue; and they have a high milk/plasma ratio. Heptachlor shares all these attributes of the other organochlorine pesticides (Wilson et al., 1980; Wolff,1983). It also shares the attribute that typical levels in breast milk exceed the acceptable-daily-intake (Rogan et al., 1980; Wolff, 1983). This is true when exposure is only through typical environmental background levels (Pfenninger et al., 1984; Wolff,1983). The acceptable-daily-intake is exceeded by orders of magnitude, however, when there is occupational exposure or a specific contamination incident such as occurred in Hawaii (Norton, 1982; Wolff, 1983).

Matsumura (1975) wrote that breast-fed infants are most at risk from exposure to organochlorines. There are several factors which account for this. First is the fact that organochlorine insecticides are known to have a propensity to bioaccumulate or biomagnify in the food chain (Jensen, 1983; Matsumura, 1975; Rogan, 1982). As was noted previously, since the human infant can be considered to be

at the top of the food chain, infants would therefore be especially at risk (Johnson, 1982; Rogan, 1982; Rogan et al., 1980). A second factor is that the primary route of excretion of such lipophilic chemicals is through breastmilk (Hayes, 1975; Matsumura, 1975; Finberg, 1977; Jensen, 1983). This means that the mother's accumulated burden of organochlorines is available for passage through the breast milk to her infant. In fact, lactation has been found to result in mobilization of stored insectices (Adamovic, Sokic & Jovanovic-Smiljanski, 1978) and is believed to lead to reactivation of the stored agent (Ecobichon & Joy, 1982).

Risks to Infants From Contaminated Breast Milk

Environmental chemicals at these levels pose a risk to breast-fed infants on a number of grounds. Foremost is consideration of body burden. Exposure to a chemical is usually calculated in terms of weight of the individual (mg/kg body weight). The relatively small size of infants results in a larger body burden compared to adults (Adamovic et al., 1978; Hays, 1975; Johnson, 1982; Norton, 1982). When considering a lipid soluble chemical which is stored in fat, a newborn is saddled with an especially heavy burden since body fat is at a minimum (Jensen, 1983). The small amount of body fat available for storage of the pesticide results in more of the pesticide being circulated in the blood and thus able to reach various target organs such as

the brain or the liver and, thus, affect enzyme functioning (Jensen, 1983; Kroger, 1974; Rogan et al., 1980).

Subsequent growth would dilute the body burden if no further exposure occurred (Wolff, 1983). Any additional exposure is superimposed on the burden of the chemical acquired prenatally through transplacental transfer (Jensen, 1983; Finberg, 1981). Wolff (1983) estimated that the body burden of a breast-fed infant could double in the first postnatal week in terms of total residue and by the second month when increasing body size is taken into account. Rogan (1982) cautioned that chemicals stored in fat as body burden should not be assumed to be inactive. He asserted that their effects would be subtle and not detectable by present epidemiologic methods. As stated previously, since the remaining life expectancy of children exposed through breast-feeding is 70 or more years, these agents have a maximal period in which to express their effect (Omenn, 1982). Weil, in a discussion published as part of Kimbrough (1982a) observed that a substance stored over years in the body may have a very different effect from one that is cleared rapidly from the body.

A second factor contributing to the increased risk status of the infant is that the young infant's diet consists only of milk, an amount of milk that in relation to body weight is equivalent to an adult consuming 10-20 quarts of milk a day (Eichorn, 1979). Quinby, Eichorn and Durham

(1965), in one of the earliest studies of insecticide contamination of breast milk, calculated that a breast-fed infant would be consuming 20 times the average adult daily intake of DDT. This is another argument for revision of the acceptable-daily-intake taking into account breast-fed infants (Wolff, 1983). Jensen (1983) noted that while the acceptable-daily-intake is calculated in terms of lifetime exposure, no information is available about effects from early exposures exceeding the acceptable margin of safety.

A third factor to be taken into consideration is that a number of the lipophilic insecticides and environmental chemicals such as PCB found in human breast milk are also considered to be carcinogenic (IARC, 1979). While there is no clear relationship between teratogenicity and carcinogenicity (Wilson, 1973), this adds a further dimension of concern. Since in Hawaii a substantial proportion of breast milk tested was above the FDA acceptable level for heptachlor residues in bovine milk and taking into account that acceptable limits in commercial milk do not provide an acceptable margin-of-safety for small infants (see Johnson, 1982), real carcinogenic potential of contaminants in breast milk should be considered. Jensen (1983), while asserting that there are no clear cases of harm resulting from consumption of contaminated breast milk, cited research indicating a trend of increases of childhood tumors. Infante, Epstein and Newton (1978) suggested that

there is an association of chlordane and heptachlor with childhood neuroblastomas and aplastic anemia. Thorough epidemiological research is needed to determine if, in fact, there is an increase in childhood cancers which parallels the increased contamination of human breast milk (Jensen, 1983). An especially important question is whether the population of children in Hawaii exposed prenatally and through lactation to heptachlor will experience a higher incidence of tumors as might be predicted from the animal literature.

The importance of the postnatal period in brain development is another factor relating to contamination of breast milk. The period of breast feeding coincides with what is considered to be a critical period of brain growth. As was noted earlier in the discussion of critical periods, birth does not constitute a boundary of susceptibility to damage. An additional consideration is that the lipids in breast milk to which the heptachlor is attached are essential in brain development and myelinization of nerves (Chapman, 1972; Gyorgy, 1971; Jelliffe & Jelliffe, 1978) which continues at a rapid pace until the end of the second year (Gilles, Shankle & Dooling, 1983). Gilles (1983a) speculated that the rapid deposition of myelin during this period may make the brain "susceptible to a unique class of insults" (p.3). Furthermore, the blood-brain barrier is much more permeable at this stage (Dhopeshwarkar, 1983)

rendering it more accessible to environmental chemicals (Brackbill, 1979, O'Mahoney, 1982). Since the CNS is the site of action of most insecticides (Hayes, 1982) and since the brain is relatively undeveloped both morphologically and functionally at birth (Brackbill, 1979; Dobbing & Sands, 1973) it is, therefore, more vulnerable to insult (Dobbing, 1972; Giles, 1983b; Langman et al., 1975).

The liver and kidney in the neonate are also still developing and, thus, are not able to deal efficiently with toxic agents (Brackbill, 1979; Jensen, 1983). It has been suggested that the fetus and neonate are more sensitive to toxic effects because of the immaturity of drug metabolizing mechanisms (Allen et al., 1979; Horning, Butler, Nowlin & Hill, 1975; Pelkonen & Karki, 1973). There is a question still to be answered as to whether insult to the liver or kidney while functionally immature will affect future development. For example, Garfunkel (1982) suggested that the increased incidence of biliary atresia in rural areas may be the result of pesticide exposure. The fact remains that organochlorine insecticides do affect adult liver function and their presence in breast milk may have an impact for functional and morphological development of this organ.

It becomes obvious that contaminated breast milk poses a threat to optimum development of the nursing infant. As was stated previously, no instances of deleterious outcome

have been known to result from consumption of breast milk contaminated with organochlorine insecticides. However, Bagnell and Ellenberger (1977) reported obstructive jaundice and heptatomegaly in a 6-week-old breast-fed infant as a result of her mother's exposure to an aromatic chlorinated hydrocarbon. Since the mother's liver functioning was completely normal, the authors speculated that the infant liver may be more vulnerable to the effects of chlorinated hydrocarbons.

Given the present state of knowledge of the effects of consumption of contaminated breast milk by infants, it is still recommended that, unless contraindicated, mothers consider nursing as the feeding method of choice (Barr, 1981; Finberg, 1977; Jelliffe & Jelliffe, 1978; Miller, 1977; Wolff, 1983). However, high levels of environmental agents are considered to be an obvious and major contraindication to breast feeding (Barr, 1981; Finberg, 1977; Rogan et al., 1980). Additionally, it is recommended that caution be exercized when there has been occupational exposure (Wolff, 1983). It has been suggested that programs of weight reduction be avoided by nursing mothers to avoid mobilization of the chemicals stored in adipose tissue (Rogan et al., 1980) since the energy demands of lactation already tend to reactivate these agents stored in adipose tissue. It is believed that reactivation can lead to levels in the blood sufficient to cause toxic symptoms (Ecobichon &

Joy, 1982). It is also advised that pregnant and lactating women not consume sport fish in order to avoid increasing their body burden of environmental contaminants (Miller, 1977; Rogan et al., 1980). Since more women are choosing to breastfeed their infants, the widespread contamination of human breast milk by a variety of agents necessitates further research on the consequences, bearing in mind that sequelae may be subtle, difficult to detect or latent.

Environmental Agents Demonstrated to be Behavioral Teratogens

While there is no scientific literature specifically dealing with the impact of prenatal and lactational exposure of humans to heptachlor, examples exist of equivalent exposures to other environmental contaminants. Lead, mercury, PCBs (polychlorinated biphenyls), and PBBs (polybrominated biphenyls) have all been investigated for behavioral teratogenesis in humans. Golub and Golub (1980) noted that long-term and low-level gestational and lactational exposures to these environmental chemicals place infants at greatest risk.

The pervasiveness of lead in our environment resulted in its being one of the first enviromental pollutants to be examined as a behavioral teratogen. Byers and Lord (1943) found that children who had been hospitalized for lead poisoning had long term behavioral sequelae such as

difficulty in school, problems with fine sensorimotor movements, distractibility, emotional lability and irritability. While this study lacked a control group and only included children with overt signs of lead poisoning, it was considered seminal in its consideration of behavioral consequences of lead ingestion. Subsequent studies of long term effects of early lead ingestion have experienced difficulty in determination of the extent of previous exposure (Weiss, 1983). Needleman et al. (1979) solved this problem by using lead levels in the baby teeth of primary school children as an index of cumulative lead exposure. When children with high and low levels in deciduous teeth were compared, high lead children performed more poorly, especially in the areas of verbal and auditory processing. In addition, the high lead group experienced more problems with attention and classroom behavior (Needleman, 1982). While the difference between the IQ scores of the two groups was statistically significant, the actual means differed by only 4.5 points. However, Needleman et al. (1982) noted that this small shift in the distribution of scores resulted in high lead children being more likely to have IQs less than 80 and less likely to have IQs higher than 125. Needleman (1982) supported his findings of detrimental effects of lead exposure by subsequent reanalysis of his data. In newborns, Needleman, Rabinowitz and Leviton (1983) reported that minor physical anomalies were associated with

levels of lead in umbilical cord blood. Needleman, Bellinger, Leviton, Rabinowitz and Nichols (1983) discovered in following a group of infants for one year that the Bayley Mental Development Index was inversely related to cord blood lead levels. Shaheen (1984) found that the specific sequelae of lead exposure were determined by age at exposure.

Animal research on lead exposure supports the findings of human research (Weiss, 1983). While effects on learning and activity have been found, the major effects seem to be on response inhibition and motor coordination (Golub & Golub, 1980).

Mercury has been firmly established as embryotoxic in humans (Wilson, 1977b). Kurzel and Cetrulo (1981) reported that no other human teratogen has had as many victims as methylmercury. Numerous incidents have resulted from the consumption of seed grain treated with methylmercury as a fungicide. The most extensive such incident occurred in Iraq where approximately 50,000 people were poisoned and 5,000 died as a result of eating the contaminated grain (Weiss, 1983).

Discharge of mercury into water has also led to contamination of fish (Kurzel & Cetrulo, 1981). Consumption of highly contaminated fish resulted in the poisoning of hundreds of people in Minamata, Japan. This incident demonstrated that infants are more susceptible to harm from

methylmercury than are adults. Newborn infants accounted for a disproportionate number of the mortalities (17%). In addition, a number of infants were born with cerebral palsy to mothers who had had no, or only minor, symptoms of poisoning (Harada, 1977). Kurzel and Cetrulo (1981) attributed methylmercury's effects to its affinity for the CNS and its tendency to accumulate in the fetus with the concentration in the fetal brain and blood several times that found in the maternal brain and blood. Weiss in a discussion published with Weiss and Clarkson (1982) stated that the fetus protected the mother from mercury poisoning, in effect, acting as a "sink". That is, the fetus traps the mercury after it crosses the placenta (Kurzel & Cetrulo, 1981).

The Iraq incident allowed more extensive evaluation of the effects of methylmercury, and the nature of the incident permitted evaluation of postnatal exposure through lactation (Weiss, 1983). Clarkson et al. (1981) found the exposed infants to have defects in speech and motor development, as well as overall retarded development. Weiss and Clarkson (1982) presented evidence showing that infants exhibited neurological damage at 1/3-1/4 the dose at which mothers exhibited similar signs. A longitudinal study of breast-fed infants provided evidence that lactational exposure also can produce brain damage and mental retardation (Amin-Zaki et al., 1981). It is predicted that once these children enter

school, their disabilities will constitute an even larger handicap (Weiss, 1983).

Due to the world-wide contamination of fish with methylmercury as a result of discharge into water and also as a consequence of acid rain, concern about mercury's teratogenic effects is not limited to these areas where there was a specific contamination incident. More circumscribed exposures have also occured. Pink disease (acrodynia) in young children was discovered to be due to the use of teething powders containing mercury (Warkany & Hubbard, 1951). More recent evidence has emerged of mercury contamination of incubators as the result of broken thermometers (Waffarn & Hodgman, 1979).

Animal research has confirmed the neurotoxicity of methylmercury as well as its teratogenicity. Studies have shown behavioral involvement in mice treated with methymercury (Spyker & Smithberg, 1972; Spyker, Sparber & Goldberg, 1972) with behavioral deficits increasing with age (Spyker, 1975).

PCBs are another ubiquitous contaminant of the environment which have been implicated as teratogenic (Golub & Golub, 1980; Kurzel & Cetrulo, 1981). PCBs are used in transformers, plastics and carbonless carbon paper and are known to be extremely persistent in the environment, lipophilic and poorly metabolized. A major human exposure to PCB occurred through contamination of cooking oil in

Kyushu, Japan. In adults consumption resulted in chloracne, headache, nausea and diarrhea (Kurzel & Cetrulo, 1981). Infants exposed prenatally had a characteristic brown pigmentation (cola-colored) and tended to be small-for-gestational age and born prematurely (Harada, 1976; Miller, 1977). Two of the 13 prenatally exposed infants were stillborn (Kuratsune, Yoshimura, Matsuzaka & Yamaguchi, 1972). Breast-fed infants tended to have higher levels of PCB in serum and tissues 13 years later (Harada, 1976). Growth impairment in these children was accompanied by mental retardation, clumsiness, hypotonia and apathy (Harada, 1976). This constellation of symptoms has been labelled "yusho" or rice-oil disease.

Careless disposal of this nonbiodegradable substance has also resulted in contamination of both soil and water and bioaccumulation in fish (Jacobson et al., 1984; Kurzel & Cetrulo, 1981). Consumption of contaminated fish has been shown to result in higher serum levels of PCBs (Schwartz, Jacobson, Fein, Jacobson & Price, 1983). Jacobson et al. (1984) have found motoric immaturity, poorer lability of states, more startle responses as well as hypoactive reflexes in infants to be correlated with contaminated fish consumption by mothers. Consistent with the findings from Japan, prenatal exposure was also found to be related to small-for-gestational age and lower gestational age in some infants. Expression of symptoms in this study was considered

by the authors to reflect individual susceptibility to PCBs (Jacobson et al., 1984).

PBB belongs to the same chemical family as PBC and shares many of its characteristics although PBB is not as ubiquitous a pollutant. However, widespread contamination of the food supply and, consequently the population, of the state of Michigan occurred beginning in 1973 when a fire retardant was mistakenly mixed with cattle feed. Analysis of samples of breast milk indicated that PBB contamination had spread beyond the farms using contaminated feed to the general population of the state (Reich, 1983). Pediatric examination of exposed children has not revealed any specific pattern of physical or behavioral symptoms related to PBB exposure (Barr, 1980; Weil, Spencer, Benjamin & Seagull, 1981). However, behavioral testing of a small sample of exposed children has shown scores on certain tests to be related to fat levels of PBB. Seagull (1983) found that children with a higher body burden of PBB scored lower on four subtests of the McCarthy Scales of Children's Abilities than did children with lower body burdens of PBB. Schwartz and Rae (1983) when testing the same children 2 to 3 years later with the complete McCarthy found that scores for these exposed children fell within the normal range although an inverse relationship was found between PBB levels and some of the subscales of the test. They concluded that overall there were no effects of PBB

exposure, despite finding some negative relationships between PBB levels and performance. Comparison of these two studies is difficult because of methodological differences between them. Therefore, it is not possible to judge whether the effect of PBB was specific to the age range of the Seagull study (between 2 1/2 and 4) or whether the results are due to the methodological differences (Nebert, Elashoff & Wilcox, 1983). Even in the face of these problems, Nebert et al. (1983) emphasized the necessity for continued behavioral and physical monitoring of individuals highly exposed to both PCB and PBB.

Despite the ubiquity of insecticides in the environment, and their now routine detection in breast milk, no human studies have been conducted on behavioral effects of gestational and/or lactational exposure. This is probably in part due to the previous absence of any circumscribed accidental exposures. At the present time research is in progress on behavioral effects of insecticide exposure in a population with only routine exposure (W. J. Rogan, personal communication, 1983).

However, some animal literature exists on behavioral effects of exposure to pesticides. Revzin (1970) in a study of the effects of chronic exposure to endrin in monkeys reported that although seizure threshold was affected, the only overt sign of poisoning was hyperirritability.

However, four months after cessation of exposure stress induced seizures occurred.

Spyker and Avery (1977) found that prenatal exposure to diazinon resulted in subtle behavioral dysfunctions which were only apparent later in development of the mice. However, among exposed animals, it was observed that the level of exposure affected the pattern, but not the magnitude of behavioral deficts.

Although Al-Hachim (1971) was not able to demonstrate an effect of prenatal exposure to aldrin on conditioned avoidance in mice, a significant effect on seizure threshold was seen. However, Van Gelder (1972), Chambers (1982) and Burt (1972) all reported behavioral changes in animals after postnatal exposure to dieldrin. Van Gelder (1972) demonstrated that while no effect was seen on simple tasks, dieldrin exposure adversely affected relearning of a visual discrimination and signal detection. Chambers (1982) after dosing a dog with .4 mg/kg dieldrin for two years discovered that the animal developed an abnormal gait and displayed leg cocking while running. In addition, EEG changes were seen. Burt (1972) reported that a DRL (differential reinforcement of low rate) operant schedule was sensitive to effects of dosing with dieldrin.

Al-Hachim and Fink (1968) found that prenatal exposure to DDT resulted in difficulty of acquisition of a conditioned avoidance response in mice. Woolley (1970)

reported that prenatal DDT exposure also slowed development of the nervous system as evidenced by later acquisition of the startle response and the righting reflex.

In another experiment Al-Hachim and Al-Baker (1973) suggested that prenatal chlordane exposure, like DDT, affected conditioned avoidance acquisition, but additionally, affected electro-shock threshold and open field behavior in mice. It should be noted that in these studies prenatal exposure also resulted in postnatal exposure since these chemicals are excreted in milk. No cross-fostering was used to separate prenatal from postnatal effects or to control for secondary effects although it has been suggested that this be a routine part of such studies (Spyker, 1975, 1975a).

It should be made clear that, as noted previously in relation to teratogens in general, the mechanisms responsible for these effects are unknown (Chambers, 1982; Kimbrough, 1982; Spyker & Avery, 1977). Researchers in this field are still attempting to delineate sequelae of exposure to environmental chemicals. Explication obviously cannot precede discovery of the phenomena.

Ecobichon and Joy (1982) concluded after reviewing research on the behavioral effects of exposure to insecticides that simpler tasks required a higher level of exposure for disruption of performance. More difficult learning tasks or complex behaviors seemed to be more

sensitive to behavioral disruption by pesticide exposure. Differential susceptibility of the learning tasks to disruption was also demonstrated by the studies reviewed here. Burt (1972) argued that chronic effects could not be effectively evaluated with mazes, but that the free operant situation is a more sensitive a measure. He maintained that such methodology would be able to reflect behavior changes at lower doses as well as enabling study of long term, often multiple exposures which are more analagous to the human situation. Van Gelder (1972) likewise concluded that some experimental tasks are less sensitive than others for detecting subtle behavioral alterations. Golub and Golub (1981) hypothesized that tertologic damage would be reflected in the ability to suppress ongoing, preferred, or previously learned behavior and, therefore, tests which require some sort of inhibition of behavior would be most likely to reflect this deficit. It is well recognized that detection of effect often depends on criterion measure. The number of articles addressing this issue reflects the cognizance of its importance in behavioral teratology (see Barlow & Sullivan, 1975; Coyle et al., 1976; Rodier, 1978).

The Present Study

The contamination of the milk supply of Oahu, Hawaii created a situation in which teratological effects were possible. The contaminant, heptachlor, is extremely

persistent in the environment and bioaccumulates in the food chain. It is a poorly metabolized lipophilic chemical which crosses the placenta readily. Its major route of excretion is through breast milk resulting in further exposure of breast-fed infants. Although heptachlor has not been shown to be a human teratogen, similar environmental contaminants have been demonstrated to have detrimental effects on prenatally exposed infants.

A naturally occurring experiment such as this presents an excellent opportunity to study the effects of an environmental toxin on the development of infants. Scientific responsibility requires using this situation not only to further knowledge about consequences of such an exposure, but also to address questions of a concerned community.

While no information exists about heptachlor's effects, factors related to teratologic outcome have been elucidated. The present study was designed to address the important dimensions of timing, dosage and duration of exposure. Assessment was made of the physical and behavioral development from birth through 12 months of a group of infants potentially exposed to heptachlor prenatally through the milk their mothers consumed during pregnancy and/or postnatally via breastfeeding.

Because of the nature of the exposure, it was not anticipated that gross physical defects or substantial

mental retardation would result. Rather, it was hypothesized that any behavioral or physical changes resulting from exposure to heptachlor would only become apparent when the combined impact of a number of variables was considered. Consequently, the data were examined in the perspective of a multiple effects model in which a matrix of predictor variables and their association with a matrix of criterion variables were considered. This method allowed evaluation of the effect of a cluster of variables including exposure to a toxic and potentially teratogenic agent on physical and behavioral development as suggested by Weiss (1983).

The major variables of concern in the present study were duration and timing of exposure to heptachlor and the level of exposure to heptachlor. Three categories of outcome variables were assessed: 1)physical and health variables at birth, 2) postnatal physical and health variables, i.e., growth of the infants and subsequent serious illnesses and hospitalization, and 3) performance on behavioral tests. These categories of variables reflect the three possible non-lethal results of exposure to a teratogen: morphological anomalies, growth retardation and functional abnormalities.

While precise apriori predictions of effects could not be made, this study was designed to address issues of importance suggested by the literature:

1) Will there be patterns of effects dependent on duration, timing and level of prenatal exposure?

2) Will perinatal variables reflect effects of prenatal exposure to heptachlor?

a) Will the effects of heptachlor vary with trimester(s) of exposure?

b) Will effects vary with level of exposure?

3) Will the physical/health measures of growth and subsequent serious illness and hospitalization be affected by extent of heptachlor exposure?

a) Which dimension, if any, of exposure to heptachlor has the strongest effect on physical/health variables: prenatal duration and timing, prenatal level, postnatal level, or postnatal duration?

b) Will growth effects, if they occur, be reflected in a single variable, or will overall growth be affected?

c) Will a specific cluster of illnesses be related to heptachlor exposure, or will morbidity in general be influenced?

4) Will performance on neonatal and infant behavioral and developmental tests be affected by heptachlor exposure?

a) Again, which, if any, dimension of heptachlor exposure will affect performance?

b) Will effects be global, or specific to a certain scale?

c) Will effects, if any, be long term, or will effects be age specific?

METHOD

Subjects

A total of 120 infants (60 males and 60 females) born at a health-maintainence-plan hospital in Honolulu, Hawaii during the months of March, June and September, 1982 participated in the study. Inclusion in the study was determined by: 1) maternal age of at least 18 years, 2) maternal fluency in English sufficient for interview and 3) willingness of the mother to allow testing of her infant over the 18 months following delivery.

The ethnic diversity of the state was reflected within the study sample so that a wide range of ethnic groups were included (see Table 1). Other demographic and anthropometric characteristics of the mothers are shown in Table 1. Mean age of the participating mothers was 27.9 years (S.D. 5.1) and the mean number of years of residency in Hawaii was 18.9 (S.D. 10.7). Occupational score and social status index score were derived using the Hollingshead Two Factor Index of Social Position (Hollingshead, 1957). Years of education and occupational rating for the parent at the highest level was used to determine the social status index score. It was reasoned that social position would be determined by the education and occupation of the parent at the higher level, not necessarily by the occupation and education of the father.

Table 1

Maternal Characteristics

Ethnic Group Membership

	Caucasian	Pacific Islander	Oriental	Filipino
N	54	2	19	7
%	45.0	4.2	15.9	5.8

	Mixed with Caucasian	Mixed with No Caucasian	Other
N	24	9	2
%	20.0	7.5	1.7

Years of Education

	Less Than 12	High School Graduate	Some College	College Graduate	Graduate School
N	5	39	34	25	17
%	4.2	32.5	28.3	20.8	14.2

Occupation (Hollingshead Categories)

	1	2	3	4	5	6	7
N	0	28	20	29	13	4	26
%	0	23.3	16.7	24.2	10.8	3.3	21.7

Social Status (Hollingshead Categories)

	1	2	3	4	5
N	16	40	44	13	7
%	13.3	33.3	36.7	10.8	5.8

Para

	0	1	2	3	4	5
N	55	42	13	8	1	1
%	45.8	35.0	10.8	6.7	.8	.8

Gravida

	1	2	3	4	5	6
N	31	46	25	9	7	2
%	25.8	38.3	20.8	7.5	5.8	1.7

Using this method of determination, the mean score of the total group was 2.63.

Twenty-seven of the mothers reported consuming alcohol with the mean ounces consumed per week being 12.8 (range 2-84). Twenty-four mothers smoked with a mean of 10.9 cigarettes per day (range .3- 25). The mean number of drugs taken was 1.8. Four mothers reported taking no drugs at all and 52 reported use of drugs other than vitamins and tylenol, e.g., antibiotics, antihistamines. Only four mothers reported recreational use of drugs. Thirty-eight of the mothers had no illnesses during gestation, and the remaining 82 had a mean of 1.7 illnesses (range 1-9). (A listing of the types of illnesses and their frequency may be seen in Appendix A.) Twenty-three percent of the mothers had had one abortion while 10 percent of the sample had more than one.

Of the participating mothers, 98 (81.7 %) breast-fed for at least two weeks while 22 infants were exclusively bottle fed. Sixty mothers were breast feeding for the first time while 37 had nursed other children (one mother: no data) with a mean duration of the previous nursing of 7.5 months (range .5 -24.0). Only 30 of the nursing mothers gave supplemental bottles during the first month with the mean number of ounces per day of formula being 6.95 (range 0-24.0). Total number and percentage of total for each type of feeding method may be seen in Table 2 for the three birth

Table 2

Feeding Method

	March	June	September	All
Number Breastfeeding	34	29	35	98
% of Sample	85.0	72.5	87.5	81.7
Number Bottle Feeding	6	11	5	22
% of Sample	15.0	27.5	12.5	18.3
Mean Duration of Breastfeeding (months)	8.3	7.0	7.2	7.5

month groups as well as for the total sample. Included also is the mean duration of breastfeeding for each group.

Infant characteristics were not used as criteria for inclusion in the study. It was believed that restriction of the sample to normal infants, or infants above a certain gestational age or birthweight might result in the overlooking of an effect of heptachlor exposure. All subjects were single births and 55 were nulliparous. The majority of babies were born by spontaneous vaginal delivery. Frequency of specific delivery methods may be seen in Table 3.

The means and standard deviations of a variety of birth variables are contained in Table 4, both for the total group and for separate birth months. The mean birthweight of the sample was 3447.8 grams (S.D. 506.6). Mean length was 50.3 centimeters (S.D. 2.5) and mean head circumference was 34.4 cm (S.D. 1.5). Mean gestational age was 39.4 weeks (S.D. 1.7). A listing of type and frequency of delivery complications, neonatal complications and physical anomalies is presented in Table 5. Classification of delivery complications, neonatal complications and physical abnormalities as serious was made by a pediatrician involved in the project. Birthweight, length and head circumference were converted to percentile range scores according to the norms of the National Center for Health Statistics (NCHS) (1976) in order to have a second set of variables free of

Table 3

Frequency of Delivery Method

Method	N	%
Spontaneous Vaginal	79	65.8
Pitocin Induced or Augmented	19	15.8
Forceps	4	3.3
Suction Extraction	2	7.7
Primary C-Section	9	7.5
Repeat C-Section	7	5.8

Table 4

Characteristics of Sample: Perinatal Variables

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
Birthweight(g)	3462	574	3517	444	3365	495	3448	507
Head Circumference (cm)	34.5	1.3	34.5	1.1	34.1	1.9	34.4	1.5
Length (cm)	50.4	2.6	50.6	2.2	49.9	2.8	50.3	2.5
Ponderal Index	2.69	.23	2.71	.25	2.71	.38	2.70	.29
Gestational Age (weeks)	39.5	1.9	39.8	1.4	39.0	1.8	39.4	1.7
Apgar 1 min.	8.2	1.1	7.8	1.5	8.1	1.2	8.0	1.3
Apgar 5 min.	9.5	.6	9.3	.6	9.3	.8	9.4	.7
Delivery Complications	.17	.45	.45	.81	.45	.81	.36	.72
Serious Deliv'y Complications	.10	.38	.15	.36	.13	.33	.13	.36
Neonatal Complications	.30	.65	.20	.46	.52	1.20	.34	.84
Serious Neon'tl Complications	.13	.46	.15	.43	.30	.65	.19	.51
Physical Abnormalities	.23	.58	.15	.43	.28	.64	.22	.55
Serious Phys'l Abnormalities	.10	.44	.03	.16	.13	.33	.08	.33
Days in Hospital	3.6	2.5	3.0	1.3	3.0	1.7	3.2	1.9

Table 5

Type and Frequency of Delivery Complications, Neonatal Complications and Physical Abnormalities

Delivery Complications	N	* Serious
None	89	
Asphyxia Neonatal*	1	
Pre-eclampsia or Toxemia*	5	
Placental Abruption*	1	
Fetal Distress*	4	
Resusitation*	2	
Placenta Previa*	1	
Depressed Respiration*	1	
Cephalo-pelvic Disproportion	1	
Acrocyanotic	2	
Jittery	2	
Tight Nuchal Cord	4	
Premature Rupture	1	
Pharangeal Suction	5	
Precipitous Labor	2	
Meconium Below Cords	4	
Rapid Respiration	2	
Delivery at Home	1	
Variable and Late Decelerations	1	
Limp baby	1	
Other	2	

Neonatal Complications	N	* Serious
None	94	
Tachyapnea*	6	
Persistent Fetal Circulation*	1	
Entubated*	7	
Hypoglycemia*	1	
Mild Respiratory Distress*	2	
Strep*	2	
Staph*	2	
Bradycardia*	14	
Apnea*	2	
Plethoric	1	
Gram Positive Gastric Contents	2	
Irregular Heart Rate	1	
Difficulty in Maintaining Temp.	2	
Stressed Baby	1	
Anti-M Antibody	1	
Acrocyanotic	1	
Jittery	2	
Heart Murmur	1	

Table 5 cont.

Positive Coombs	1
Irritable	1
Multifocal Premature Beats	1
Floppy	1
Other	3

Physical Abnormalities	N	* Serious
None	100	
Cryptorchidism*	1	
Kleinfelter's Syndrome*	1	
Acyanotic Congenital Heart Disease*	2	
Pyloric Stenosis*	1	
Microcephalic*	1	
Cleft Palate*	1	
Cleft Lip*	1	
Floating Thumb*	1	
Bilateral Hand Abnormality*	1	
Simian Crease	3	
Loose Rectus	1	
Foot Crease	1	
Preauricular Tags	1	
Tongue Abnormality	1	
Heart Murmur	1	
Brachycephaly	1	
Epicanthal Eye Folds	1	
Low Ears	1	
Hydroculi	2	

the influence of gestational age. The distribution of these scores for each month and for the total sample may be seen in Table 6. A Ponderal Index (an index of appropriateness of weight for length) was also calculated for each infant. Ponderal Index is birthweight in grams multiplied by 100 divided by length in centimeters cubed (Miller & Hassanein, 1971). Since heptachlor and heptachlor epoxide potentially may affect liver functioning, jaundice was examined as a separate category of neonatal complication. Table 7 displays the total number of cases of jaundice, mean bilirubin level (when analyzed) and classification of jaundice by separate month, as well as for the sample as a whole.

Infants born in March, June or September experienced different durations and trimesters of exposure to heptachlor. The March infants were exposed for three trimesters, their entire gestation, the June babies for two trimesters and the September babies for only one trimester. When the study was designed, contamination of the commercial milk supply was thought to have been limited to the period January-March 1982. If this had been true, each group of subjects would have represented a different trimester of exposure. However, it was discovered after the testing of the first two groups of infants that the contamination extended back at least to January, 1981 (Smith, 1982). Consequently, in this study the variable of birthmonth

Table 6

Characteristics of Sample: Birthweight, Head Circumference and Length Percentile Range Scores Using NCHS Norms

MARCH

Birthweight						Head Circumference						Length					
1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
0	0	5	18	7	10	0	3	7	5	20	5	0	3	8	5	16	8

M=4.55 S.D.=1.01 M=.4.43 S.D.=1.15 M=4.45 S.D.=1.24

JUNE

Birthweight						Head Circumference						Length					
1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
0	1	7	11	10	11	0	3	7	6	19	5	0	2	6	8	14	9

M=4.57 S.D.=1.15 M=4.40 S.D.=1.15 M=4.56 S.D.=1.17

SEPTEMBER

Birthweight						Head Circumference						Length					
1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	3	4	11	11	10	3	3	6	9	11	8	1	4	6	6	17	6

M=4.45 S.D.=1.32 M=4.15 S.D.=1.50 MX=4.30 S.D.=1.32

TOTAL

Birthweight						Head Circumference						Length					
1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
1	4	16	40	28	31	3	9	20	20	50	18	1	9	20	19	47	23

M=4.53 S.D.=1.16 M=4.33 S.D.=1.27 M=4.44 S.D.=1.24

Percentile Range Scores	
	1 < 10 %ile
10 %ile ⩽	2 < 25 %ile
25 %ile ⩽	3 < 50 %ile
50 %ile ⩽	4 < 75 %ile
75 %ile ⩽	5 < 90 %ile
90 %ile ⩽	6

Table 7

Characteristics of the Sample: Jaundice

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
Bilirubin Level	12.3	1.8	12.0	3.8	13.8	2.9	12.5	3.0
Total Cases	16		14		15		45	
Types of Jaundice:	Frequency							
Unspecified	15		10		11		36	
Physiologic	0		4		3		7	
Major Blood Group Incompatibility	0		0		1		1	
Breast Milk	1		0		0		1	

represents both duration of exposure and trimester of exposure.

Procedure

Exposure to Heptachlor

Mothers who had given birth at the participating hospital in March and June were contacted by telephone to arrange an initial interview. Those agreeing were interviewed in their homes. Mothers giving birth during September were initially interviewed during their stay in the hospital. All interviewing was done by the experimenter.

During the interview a diet history was taken of the typical daily consumption of milk and milk products during the months of January-March 1982. Sample glasses, containers and a plastic model of a 4 oz. scoop of ice cream were used to assist in the estimation of amount consumed of each of 12 milk products. Consumption ranged from no milk or milk products to 64 oz. of whole milk per day. The questionnaire used was derived from the one used in the National Study of Levels of Chlorinated Hydrocarbons in Human Milk (Savage, 1976). When 12 mothers were reinterviewed, a .98 correlation was found for consumption estimation. Because of concerns about inflation of reliability, a second set of 16 mothers was interviewed and reinterviewed with a different set of sample containers used for each interview. Correlation was again found to be .98.

In addition, the accuracy of estimation using the sample set of containers was evaluated. A correlation of .92 was found between amount that the mothers estimated and true amount in sample containers. During the initial interview, additional health and demographic data were obtained. (See interview questionnaire in Appendix B.)

Although there is no doubt that the population of Oahu was exposed to the neurotoxin heptachlor via milk, a major difficulty in any food or diet related exposure is estimating individual intake (Block, 1982). The issue of the validity and reliability of food intake estimation has been addressed frequently in both the epidemiology and nutrition literatures (Becker, Indik, & Beeuwkes, 1960; Block, 1982; Burk & Pao, 1976; Kransler et al., 1982a; Pekkarinen, 1970). The specific method used within this study was a diet history in which women were asked to indicate their daily consumption of milk at a specific time in their pregnancy. The diet history was developed by Burke and Stuart (1938) in an attempt to determine pattern of usual food intake. It is considered to be a reasonably reliable method (Block, 1982; Pekkarinen, 1970). Within this study reliability was found to be quite good, test-retest r=.98. However, of equal concern is the validity or accuracy of this method.

The question of validity consists of two issues: 1) Were the women able to accurately estimate the amount of

milk they drank, and 2) Did they actually consume as much as they indicated? Steps were taken to ensure as much as possible the accuracy of estimation. As has been suggested (Block, 1982; Pekkarinen, 1970), sample glasses and food models were used to aid in estimation. A check on accuracy of estimation was made which found a correlation of .92 between amount mothers estimated they drank using model glasses and amount they indicated they drank using their own glass. However, the question still remains whether they actually consumed the indicated amount of milk. While actual daily consumption of milk and milk products is impossible to prove (Becker et al., 1960; Block, 1982), research literature in food intake assessment suggests several reasons why the present questionnaire should be reasonably accurate in reflecting the actual amount of milk and milk products the mothers consumed. Becker et al. (1960) asserted that recall of food consumption associated with important life events such as pregnancy will be more accurate. For example, Landesman-Dwyer et al. (1983) found that women were able to recall smoking and alcohol consumption during pregnancy five years later. In specific reference to the heptachlor exposure in Hawaii, it would be likely that recall of milk intake would be highlighted for pregnant women.

Furthermore, there is general agreement that frequently eaten foods are recalled more accurately (Jain, Howe,

Johnson & Miller, 1980; Kransler et al., 1982b; Nomura, Hankin & Rhoades, 1976). Milk consumption seems to be recalled especially well (Jain et al., 1980; Trulson, 1957) andaccuracy of milk intake recall has been attributed to the fact that it is regularly and frequently consumed (Kransler et al., 1982b). Since the mothers within this study were being asked to remember milk consumption during pregnancy after a widely publicized announcement of milk supply contamination, recall would be expected to reflect their intake reasonably accurately.

Correlation of heptachlor intake estimates derived from the milk questionnaire with breast milk levels of heptachlor provide another method of validation of the questionnaire. While there should be significant correlation between breast milk levels and intake of a drug, a number of other factors influence excretion in breast milk: pharmacokinetic properties of the chemical (Wilson et al., 1980); body burden of the chemical (Adamovic et al., 1978; Jensen, 1983), body weight of the mother (Polishuk et al., 1977), dieting in the mother (Eckenhausen et al., 1981), smoking (Jensen, 1983), exposure to other drugs and chemicals (Wilson et al., 1980) and fat level in milk (Jensen, 1983; Wilson et al., 1980) which itself is influenced by prior nursing experiences (Jelliffe & Jelliffe, 1978), length of lactation (Jensen, 1983), time when sample was obtained during a single breastfeeding (Baum, 1980) and even

gestational age of the child (Guerrini, Bosi, Chieri & Fabbri, 1981). The highest correlation between intake and milk levels was expected and seen in the March group ($r=.54$, $p=.01$) who had consumed contaminated milk throughout their pregnancy. The finding of heptachlor in milk of mothers who did not consume contaminated milk is not unexpected, nor does it invalidate the milk questionnaire since pesticides are found in the milk of mothers with no special exposure (Savage, 1976, in press; Tanabe, 1972). In fact, Wolff (1983) noted that the highest levels of chemicals found in the breast milk of the unexposed population overlap with the lower end of the range found in mothers with occupational or known exposures.

Daily consumption of heptachlor epoxide was calculated for each mother. This value was obtained by converting ounces consumed to liters, multiplying amount consumed of each product by the percentage fat in the specific product to determined lipid consumed per day. Lipid content of each product was obtained from the Commissioner of Milk of the State Board of Agriculture (R.S. Matsuura, personal communication, September 28, 1982). This value was then multiplied by 1.2 ppm, an estimate of the level of heptachlor in commercial bovine milk on a lipid basis. Since there was no systematic monitoring of milk levels of heptachlor epoxide during the time period of interest, an estimate had to be made taking into account the few actual

values available. A level of 1.2 ppm was considered by the EPA to be a reasonable worst case value, that is, "probably higher than the true average heptachlor level, but lower than the highest heptachlor concentration" (Johnson, 1982). J. W. Hylin (personal communication, April, 1983) and T.R. Norton (personal communcation, January 5, 1984) also considered 1.2 ppm to be a reasonable estimate of heptachlor level in commercial bovine milk on a lipid basis in the time period of interest. The value resulting from this calculation expressed as mg/day was considered to be an estimate of the amount of heptachlor consumed per day by a specific mother during January, February and March, 1982. Mean ingestion per day was .028 mg (S.D.=.024). Since dosage data are typically transformed to reduce skewness (Chan et al., 1982), the variable of mg of heptachlor consumed per day was transformed by (x + 1)log10. Although skewness in the original data was not severe (1.08), the transformed values were used in all statistical analyses in accordance with typical practice in toxicology.

Breast milk was obtained from those breastfeeding mothers able to provide a sample. Milk was expressed into pesticide free bottles (i.e., sterilized and rinsed in acetone). See Appendix C for instructions given to mothers on milk expression. Samples were analyzed by the Pesticide Hazard Assessment Project of the Pacific Basin Research Corporation at the University of Hawaii. Protocol followed

in analysis of milk was that specified by the EPA (EPA, 1980a) and used in both national studies of hydrocarbons in human milk (Savage, 1976, in press). Quality control methods were those specified by the EPA (1981).

Heptachlor epoxide levels were determined using a Tracor Microtek MT-220 nikel-63 high temperature electron capture detector. Temperature settings (Centigrade) were: column 210, detector 260, inlet 220, transfer line 260. The two columns were packed with 4% SE-30/6% OV-210 and 1.5% OV-17/1.95% QF-1. Each set of 22 breast milk samples contained 2 standard samples (Viva 2% milk) spiked with 2 ng/ml (nanogram per milliliter) and 10 ng/ml heptachlor epoxide respectively. The 2 ng sample was analyzed 19 times with a mean value detected of 2.0 ng/ml, a standard deviation of 0.2, a coefficient of variance of 10.0 % and a total error of 20 %. The 10 ng sample was also analyzed 19 times yielding a mean value of 9.9 ng/ml with a standard deviation of 1.0, a coefficient of variance of 10.1 %, and a total error of 21 %. Total error is the absolute value of the mean error plus 2 standard deviations divided by True Value and then multiplied by 100. Total errors less than or equal to 25% are considered excellent (EPA, 1981).

Heptachlor epoxide levels in breast milk were considered to reflect postnatal exposure when considered in conjunction with duration of breast feeding. The mean level of heptachlor in the breast milk samples was .118 ppm with a

range of .041-.365 ppm. All values were transformed by (x + 1)log10 for statistical analysis.

Samples of umbilical cord blood were obtained from the cooperating hospital for the babies born in June and September. See Appendix D for the protocol for obtaining samples. Procedures for analysis were those specified in EPA (1980a).

Physical/Health Measures

Medical charts of all babies born in the participating hospital in the months of March, June and September were reviewed. Data of interest were: birthweight, length, head circumference, gestational age, presence of jaundice, bilirubin level, delivery and neonatal variables, physical abnormalities, maternal age, para, gravida, abortions and length of hospital stay (see Appendix E.)

Charts were reviewed by the experimenter and an assistant trained by the experimenter. Intertester agreement was .97. Nine charts were reviewed twice to verify missing or questionable data. Correlation of these two reviews was .94. Growth data and information on subsequent serious illness and hospitalization were obtained via chart review by the experimenter and a second assistant. Agreement between raters for growth data was .92. All growth data were converted to percentile ranges using the NCHS Growth Curves (Hamill, Drizd, Johnson, Reed, & Roche,

1977). This was necessitated by the variation in the ages at which infants were taken in for check-ups. By using percentile ranges, a correction for age at examination was possible.

Behavioral Measures

Brazelton Scale

The Brazelton Neonatal Behavioral Assessment Scale (NBAS) (Brazelton, 1973) was administered to all infants in the June and September groups. March babies could not be tested since they had already exceeded the age range of the test by the commencement of the study. The NBAS is a widely used instrument which assesses behavioral capabilities of infants during the neonatal period and which has been characterized as "one of the most important developments in neonatal assessment" (St.Clair, 1978). While originally designed as a clinical tool (Brazelton, 1979), it is now very widely used in research. For a review of research uses of the NBAS see Sostek (1979) and for complete general discussion of the instrument see Als, Tronick, Lester and Brazelton (1979) and Sameroff (1979). The test consists of 20 reflex items intended to assess neurological functioning (scored 0-3) and 26 behavioral items (scored 1-9).

All tests were performed in the time period 14 to 30 days after birth with a mean age at testing of 21.3 days. Three testers were used with extensive experience in using the NBAS and who had been certified reliable on the NBAS.

Testers were blind to levels of heptachlor consumed by mothers. Due to scheduling restrictions inter-tester reliability was not determined prior to commencement of testing. It was assumed that adequate inter-tester reliability was present since the testers were using the NBAS in another ongoing research project and retention of high inter-tester reliability has been reported (Als et al., 1979; Horowitz & Brazelton, 1973). Inter-tester agreement was verified at the end of testing of the subjects. Percentage agreement was calculated by dividing the total number of agreements by the total number of agreements plus disagreements in scoring for each item. When a two point difference was allowed, percentage agreement was .84. However, when a one point disagreement was used as criterion as suggested by Als et al. (1979) agreement fell to .67.

The 44 items of the NBAS were combined into the 7 summary clusters developed by Lester, Als and Brazelton (1982): orientation, range of state, motor, autonomic stability, regulation of state and habituation. The habituation cluster was not used due to the large number of infants with missing data for this cluster. Omission of these items seems to be a common difficulty encountered in research with the Brazelton (Streissguth, Barr & Martin, 1983).

With the exception of one infant tested at home, all infants were tested either at the main pediatric clinic of

the cooperating medical plan or at the University of Hawaii Psychology Department. All infants were tested in the afternoon.

Bayley Scales

The Bayley Scales of Infant Development (Bayley, 1969) were administered at 4, 8 and 12 months. The Bayley is considered to be the best infant development test available (Kaufman & Kaufman, 1984; Sattler, 1982) and to be exceptionally well standardized (Damarin, 1978; Yang, 1979) with good reliability and internal consistency (Honzik, 1976). Yang and Bell (1975) categorized the Bayley as the most psychometrically adequate of the infant scales while Self and Horowitz (1979) described it as the most frequently used infant behavioral assessment instrument.

The Bayley Scales have been found to correlate with Apgar scores (Serunian & Broman, 1975) and with performance on the Brazelton (Crockenberg, 1983; Sostek & Anders, 1977). Correlation with later Stanford-Binet IQ scores has been reported by Bayley (1949) and Ramey, Campbell and Nicholson (1973). The Bayley Scales consist of three parts: a Mental Scale of 163 items scored pass-fail and yielding a Mental Developmental Index score (MDI), a Motor Scale of 81 items also scored pass-fail which yields a Psychomotor Developmental Index (PDI) and a Infant Behavior Record which is intended to assess the child's behavior during the testing.

Of the one hundred and twenty infants participating, 114 were tested at 4 months, 105 at 8 months and 97 at 12 months. Most drop-outs were the result of the parents' moving from the island. Only four infants were withdrawn because their parents no longer wished to participate. In several instances participation was continuued, but a specific test could not be completed because of lack of cooperation by the baby (crying, shyness, etc.). Testing site, determined by convenience for parents, was at one of the pediatric clinics of the medical group, the University of Hawaii Psychology Department or in rare instances, at the child's home. Testing was accomplished within one calender month of the child's reaching the specific age. However, when necessitated by scheduling requirements, the babies were tested prior to attaining the appropriate age. The normalized standard scores for each scale (MDI and PDI) were used in analyses rather than raw scores to eliminate the effect of age of testing.

Five testers were used. All were experienced in administration of the Bayley prior to their inclusion in this project and were blind to the extent of maternal prenatal heptachlor ingestion. Reliability for the 4 and 8 months testing calculated as phi was .825 with 92 % agreement. Inter-tester reliability for the 12 month testing was phi = .892 with 95 % agreement.

Mental development index (MDI) and physical development

index (PDI) scores were calculated for each infant test as specified by Bayley (1969). In addition, individual items in the Mental Scale were combined into five scales as suggested by Kohen-Raz (1967). These scales are: eye-hand, manipulation, object relation, imitation-comprehension, and vocalization-social contact-active vocabulary. These scales were constructed from Mental Index items using the criterion of scalability. Kohen-Raz characterized the eye-hand and manipulation scales as performance measures, the object-relation scale as reflecting conceptualization of objects and the imitation-comprehension scale and vocalization-social contact-active vocabulary scale to be indicative of language development. Siegel (1979) found differential predictability of the scales for the Stanford-Binet at 36 months depending on age of infant testing. At four and eight months the performance and conceptual scales predicted later IQ, while at 12 months the language scales became predictive of later IQ. These scores were used in the present study as more refined indices of specific developmental achievement in addition to the more global MDI and PDI scores.

There is general agreement that infant tests do not predict future functioning well (Honzik, 1976; McCall, 1979, 1982; Yang, 1979). This is true for both normal and at-risk samples (Cohen & Parmelee, 1983; McCall, 1976). However, infant tests were designed not only to predict future

competence, but also to evaluate current performance and level of development (McCall, 1976). This is sufficient to justify their use according to Prechtl (1981) who argued that these early behaviors and milestones of development should be assessed since they have contemporaneous significance for the young infant. These early behaviors are especially important in relation to evaluation of risk factors for two reasons: 1)Analysis of deviations from normal development aids in understanding the processes of development and, in the case of much infant behavior, the functioning of the nervous system (Connolly, 1981; Prechtl, 1981) and 2) They provide monitoring for infants at risk so that intervention can be initiated when appropriate (Kopp, 1983).

Statistical Analysis

The data were examined in the context of a multiple effects model encompassing a matrix of independent variables and a matrix of dependent variables. The major predictor variables of interest were amount of heptachlor consumed per day by the mother, birth month (reflecting timing and duration of exposure), heptachlor level in breast milk and duration of breastfeeding. Criterion variables fell into three general categores: perinatal variables, growth and health variables and performance on neonatal and infant behavioral/developmental tests. Since no information was available for predicting what specific physical measures or

behaviors would be affected, a large intercorrelation matrix was examined to determine possible patterns of relationships.

Inspection of this matrix revealed differential patterns of correlations of heptachlor exposure and effects dependent on birth month. These groups of variables were then explored statistically using multivariate methods in order to discover conceptually meaningful relationships. This methodology was consonant with McCall's (1970) suggested use of multivariate analyses in developmental research.

RESULTS AND DISCUSSION

Heptachlor Exposure

Milk Consumption Data

Of the 120 mothers who participated in the study 115 consumed milk and/or milk products on a regular basis during the period of January to March 1982 with an average consumption of 1.00 liter per day (S.D. .57, range 0 - 2.66 liters). In addition to the 5 mothers who did not consume any milk or milk products, 7 others indicated that their consumption of milk or milk products was limited to those products containing no heptachlor, e.g., powdered milk or mainland yoghurt. That is, ten percent (N = 12) of the participating mothers reported no ingestion of products containing heptachlor. Consumption of each milk product as well as the number of mothers reporting use of each product are presented in Table 8. Using the index described in the Methods section, mean heptachlor ingestion for the total sample was .0282 mg/day, S.D.=.0244 almost twice the acceptable daily intake of .015 mg for a 60 kg woman. In the total group values ranged from 0 to .1373 mg/day. Reported consumption for the separate months was: March mean = .0206, S.D. = .0186; June mean = .0373, S.D. = .0286; September mean = .0282, S.D. = .0244. The distribution of

Table 8

Daily Consumption of Milk and Milk Products

	Liters/Day				N of Mothers Consuming	% of Mothers	% Fat
	M1	S.D.	M2	S.D.			
Whole	.47	.57	.84	.51	67	56	3.25
2%	.16	.36	.65	.42	29	24	2.0
Skim	.09	.29	.76	.40	15	12.5	.05
Buttermilk	.01	.07	.71	-	1	.8	.05
Imitation	.04	.20	.83	.56	5	4.2	.05
Reconst'd	.06	.25	.94	.53	7	5.8	.05
Powdered	.07	.25	.77	.37	11	9.2	NC
Ice Cream	.06	.09	.10	.10	66	55	5.0-12.0*
Ice Milk	.01	.04	.16	.07	7	5.8	3.0-6.0*
Yoghurt	.03	.07	.10	.11	37	30.8	1.2-1.8*
Cottage Cheese	.02	.07	.12	.12	24	20	5.0

M1 Mean consumption by all mothers
M2 Mean consumption by those mothers consuming this product
NC No contaminated fat
* Either local or imported butterfat used in manufacturing (Cayetano, 1982; Roy Matsuura, personal communication September 28, 1982)

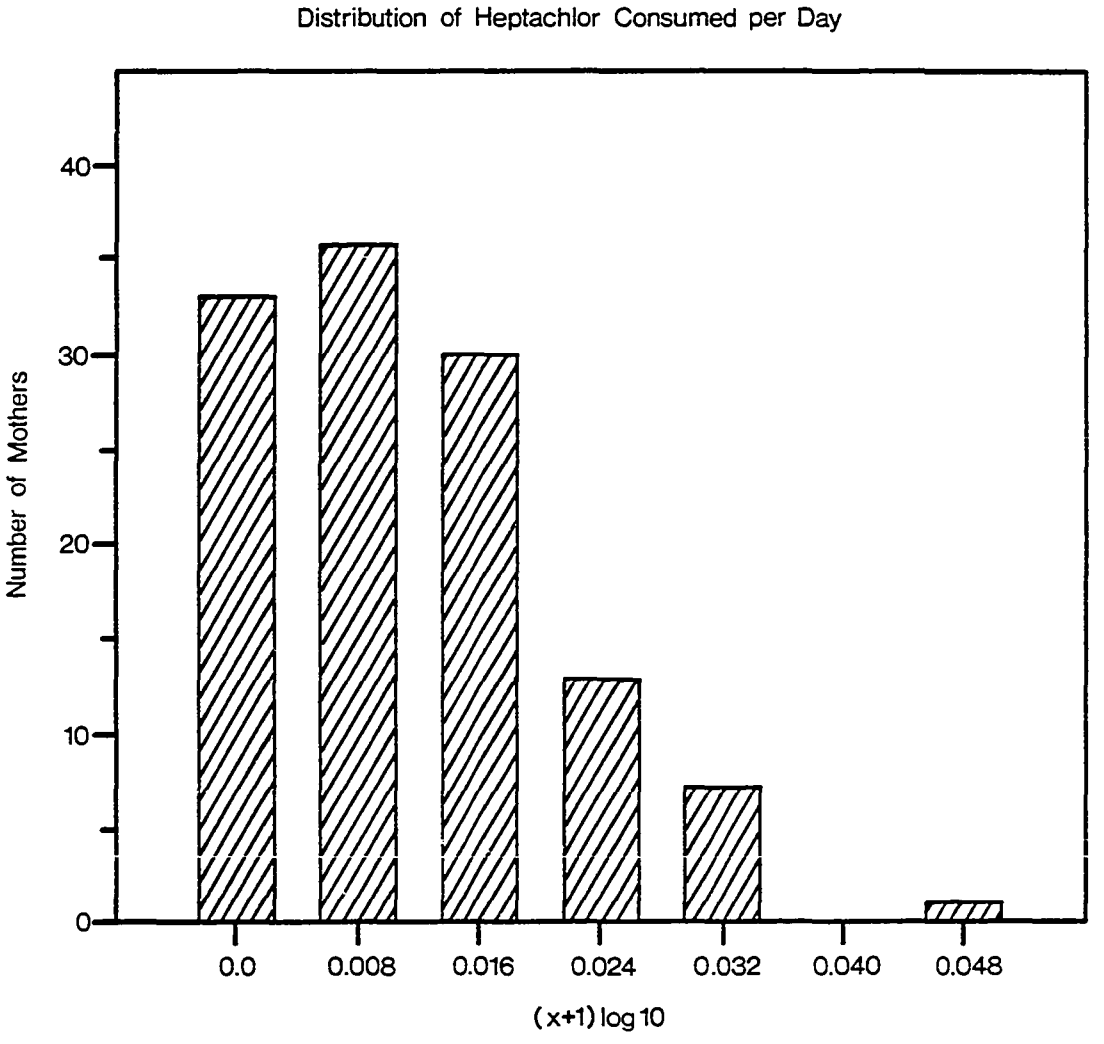
these values transformed by (X + 1)log10 may be seen in Figure 1.

Cord Blood

Samples of umbilical cord blood were obtained for babies born in the months of June and September at the participating hospital. Two sets of analyses were done: one set consisting of 20 randomly selected samples, and the second set consisting of 10 samples from mothers reporting high consumption and 10 from mothers reporting low consumption of contaminated milk. In both cases no reportable levels of heptachlor epoxide were detected. Since the literature indicated that heptachlor had been found in umbilical cord blood in a population without special exposure (e.g. Curley et al., 1969), the protocol of blood analysis used in this study was reviewed and compared with that used in previous studies (e.g. Curley et al.,1969 & Dale, Curley & Cueto, 1966). It was found that the laboratory analysis techniques were essentially identical except for the reportable levels. Curley et al. (1969) found a range of .2 - 4.3 ppb of heptachlor in umbilical cord blood. However, the quality control standards employed by the Pesticide Hazard Assessment Project (EPA, 1981) consider values below 1 ppb to be within the range of error and, therefore, not reportable.

The finding of only trace amounts (less than 1 ppb) of heptachlor epoxide in the present samples of umbilical cord

Figure 1


Distribution of Heptachlor Consumed per Day
Number of Mothers
40
30
20
10
0
0.0
0.008
0.016
0.024
0.032
0.040
0.048
(x+1) log 10

blood may be attributable to the fact that blood samples in this study were taken three (June) and six (September) months after exposure ceased. In the previous studies samples of umbilical cord blood were taken while heptachlor was still in use. Since detection of lipophilic organochlorines is difficult due to the low lipid content of serum of umbilical cord blood (Selby et al., 1969) and the tendency of levels of organochlorines in blood to dip at birth (Curley & Kimbrough, 1969), the period of time between termination of ingestion and sampling of blood may have resulted in a drop in heptachlor epoxide to non-reportable levels in the umbilical cord blood samples (EPA, 1983).

Nonetheless, prenatal exposure may be assumed based on documented evidence that heptachlor epoxide does cross the placenta since it has been found in the blood and tissues of fetuses in the absence of any extrordinary exposure (Curley et al., 1969; Polishuk et al., 1977; Zavon et al., 1969). In Hawaii there was known contamination of the milk supply and the mothers acknowledged that they consumed milk during the contamination period. Therefore, there can be no doubt that these infants were exposed prenatally to heptachlor. The EPA (1980) concluded in a review of the toxicology and health effects of heptachlor, "...any exposure of heptachlor or heptachlor epoxide to the mother will also expose the fetus to heptachlor epoxide" (p. c-12). However, it appears that although heptachlor epoxide crosses the placenta, it is

difficult to detect after periods of nonexposure. While a more accurate assessment of prenatal exposure could have been made based on analysis of infant adipose tissue, invasive techniques were not permitted.

Breast Milk

Sixty-nine of the 98 breast feeding mothers were able to provide samples of breast milk for analysis. Twenty-two of the mothers provided two samples and six of these women provided three samples. While all samples were analyzed for level of heptachlor epoxide, only first samples were included in statistical analysis due to the small number of repeat samples. It is acknowledged that a single sample of breast milk is only an approximate predictor of levels of contaminant as well as fat content. Milk composition varies both during a feeding and over the course of the day (Baum, 1980; Jelliffe & Jelliffe, 1978; Jensen, 1983) and dosage of a drug to the infant via breast milk will vary with the composition and volume of milk consumed by the infant (Wilson et al., 1980). Ideally, analysis should be based on pooled samples obtained over 24 hours (Noren, 1983). However, Jensen (1983) noted that this is impossible in most studies because of the degree of motivation in mothers necessary to obtain such samples and because such extensive collection would interfere with lactation.

Milk levels are typically expressed in terms of absolute amount ng/ml (nanograms per milliliter, a nanogram

being 10 to the -9th power) or in terms of concentration, ppm on a per fat basis. The heptachlor content in breast milk samples from the mothers in this study are reported in Table 9. While both ng/ml and ppm were calculated, ng/ml was used in all statistical analyses since this variable reflected more directly the heptachlor to which the infant was exposed without reference to amount of fat in its mother's milk.

The correlation of heptachlor consumption based on recalled milk product consumption with breast milk levels for the total sample was .27, p= .02. The highest correlation of breast milk levels and heptachlor exposure through milk consumption existed for the March group (r=.54, p= .01). The correlations for the June and September groups dropped to .31 (p= .19) and .22 (p= .27), respectively. A higher correlation between consumption and breast milk levels would be expected for March mothers who consumed contaminated milk through their entire pregnancies. Since June and September mothers consumed contaminated milk for only a portion of their pregnancies and non-contaminated milk for the remainder, their body burdens of heptachlor would be less and lower levels of heptachlor would be excreted relative to the amount of milk consumed during pregnancy.

Table 9

Heptachlor Levels, Percentage Fat, Number of Days Nursing for Breast Milk Samples

	MARCH		JUNE		SEPTEMBER		ALL	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
Ng/ml Sample 1	4.91	3.90	3.77	2.16	4.29	3.59	4.34	3.34
Ppm Sample 1	.138	.085	.138	.087	.098	.064	.123	.080
% Fat Sample 1	3.9	1.8	3.3	1.7	4.0	2.0	3.7	1.8
N Days Nursing	138	31	38	14	47	19	72	47
N of Samples	22		20		27		69	
Ng/ml Sample 2	-	-	2.93	2.67	2.80	1.78	2.79	2.22
Ppm Sample 2	-	-	.090	.089	.095	.051	.091	.070
% Fat Sample 2	-	-	3.5	1.7	3.6	2.6	3.4	2.1
N Days Nursing	-	-	156	42	147	22	160	49
N of Samples	-	-	11		10		22	
Ng/ml Sample 3	-	-	2.57	3.17	-	-	2.57	3.17
Ppm Sample 3	-	-	.104	.100	-	-	.104	.100
% Fat Sample 3	-	-	3.1	2.7	-	-	3.1	2.7
N Days Nursing	-	-	320	3	-	-	320	3
N of Samples	-	-	6		-	-	6	
HE Consumed/Day	.0206	.0186	.0373	.0286	.0265	.0224	.0282	.0244

Exposure to Heptachlor by Outcome Variable Category

The prenatal heptachlor exposure variables of concern were duration/timing of prenatal exposure represented by birth month and prenatal level of exposure to heptachlor represented by heptachlor consumption per day. Postnatal exposure variables were duration of breastfeeding and ng/ml heptachlor in breast milk. These exposure variables were examined in relation to the three categories of outcome variables: 1) Physical and health variables at birth (perinatal variables), 2) Growth and subsequent illness and 3) Performance on behavioral tests. Empirically derived, but conceptually meaningful clusters of variables within each outcome category were suggested by examination of zero-order correlation matrices. The relationship of these clusters to exposure variables was then examined using canonical correlation analysis.

In canonical correlation a linear combination of the independent variables is generated so that the correlation with a linear combination of the dependent variables is maximized. In order to understand the nature of the relationship represented by a statistically significant canonical correlation, it is necessary to examine the correlations (called loadings) of the individual variables with their canonical variates (Levine, 1977). Variables are interpreted as contributing to the relationship in the

direction and to the degree of their correlation with their own canonical variate.

Since the variable month of birth reflected the important dimensions duration and timing of exposure, four analyses were generated for each each cluster of outcome variables: one using the total subject sample and separate analyses for each birth month cohort. Differences in variable loadings on canonical variates across birth months as well as a major loading of the variable month in analysis of the total sample were interpreted as suggesting differential effects of exposure according to month.

Canonical correlations were calculated using data from subjects who had no missing data for the specific set of variables of interest. For example, if no information regarding gestational age were recorded for an infant, that subject would be completely excluded from any analysis in which gestational age was included. As a result all analyses involving the exposure variable ng/ml (heptachlor level in breast milk) utilized only data from infants whose mothers had been able to provide a breast milk sample,i.e., a subset of breast-fed infants. Consequently, it was necessary to calculate two separate canonical correlations for each cluster of outcome variables: one without ng/ml as an exposure variable and one including ng/ml with the other exposure variables. When growth and behavioral data are discussed, a distinction will be made between analyses which

included all infants and those which included only breast-fed infants. However, since perinatal variables were measured before lactation was established, heptachlor level in breast milk (ng/ml) is treated merely as an additional exposure measure in these analyses.

Perinatal Variables

Variables reflecting characteristics of the subjects at time of delivery and relating to health status during initial hospital stay are presented in Tables 4, 5, 6 and 7.

Cluster 1: Birthweight, jaundice, gestational age, number of days in hospital

As may be seen in Table 10 the zero-order correlation matrix revealed a pattern of association of exposure to heptachlor as reflected by the variable of heptachlor level in breast milk samples for the total sample with birthweight ($r=-.23$, $p=.06$), jaundice ($r=.30$, $p=.01$), gestational age ($r=-.20$, $p=.11$) and number of days in hospital before discharge ($r=.23$, $p=.06$). Canonical correlation analyses were calculated to assess the relationship between the exposure variables of prenatal heptachlor consumption, heptachlor level in breast milk and birth month with the outcome measures of birthweight, gestational age, jaundice and length of initial hospital stay.

Table 10

Zero-Order Correlation Matrix for Cluster 1 Variables

	Jaundice		Birthweight		Gestational Age		Days in Hospital	
Total	r	p	r	p	r	p	r	p
Log HE	.03	.77	.11	.23	.07	.45	-.01	.89
Log ng/ml	.31	.01	-.23	.06	-.20	.11	.23	.06
March								
Log HE	.31	.05	-.08	.63	-.10	.56	.05	.74
Log ng/ml	.54	.01	-.38	.08	-.09	.70	.25	.26
June								
Log HE	.10	.54	-.01	.97	-.04	.82	.07	.68
Log ng/ml	.04	.88	-.09	.71	-.06	.81	-.21	.38
September								
Log HE	-.26	.10	.40	.01	.26	.12	-.05	.77
Log ng/ml	.23	.25	-.19	.34	-.40	.05	.33	.09

None of the analyses for the total group or for the separate birth month cohorts reached significance when only prenatal heptachlor consumption and birth month were included as exposure variables. However, patterns of loadings of heptachlor were similar in the two sets of analyses, i.e., those with the variable heptachlor level in breast milk included as an exposure variable and those without it.

Canonical correlation analysis of these clusters of variables for the total sample of infants with breast milk samples revealed a strong but non-significant effect ($p = .08$) of lower birthweight, lower gestational age, higher rates of jaundice and longer hospital stays associated with higher levels of heptachlor in mothers' breast milk (see Table 11A). Only heptachlor in breast milk seemed to be strongly correlated with this constellation of outcomes as indicated by a loading of .98 on its own canonical variate.

When the data for March infants, i.e., those babies exposed to heptachlor throughout their entire gestation, were examined separately, the canonical correlation of heptachlor consumption and heptachlor level in breast milk with Cluster 1 variables was statistically significant ($p = .04$), (see Table 11B). For the March group, both prenatal heptachlor consumption and heptachlor level in breast milk contributed to the canonical variable and were strongly associated with higher rates of jaundice and lower

Table 11

Canonical Correlation of Heptachlor Consumed, Birth Month, Heptachlor Level in Breast Milk with Cluster 1 Birth Outcome Variables

A.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.40	.16	1.6 (12,159)	.08

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	-.17	.09
Log ng/ml breast milk	1.04	.98
Birth month	-.10	.05

Dependent Variables	Standardized Coefficients	Correlation with own variate
Jaundice	.55	.79
Birthweight	-.52	-.74
Gestational age	-.04	-.56
Days in hospital	.28	.55

Table 11 cont.

B.MARCH: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.67	.44	2.3 (8,32)	.04

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.41	.80
Log ng/ml breast milk	.72	.94

Dependent Variables	Standardized Coefficients	Correlation with own variate
Jaundice	.88	.93
Birthweight	-.45	-.55
Gestational age	.26	-.26
Days in hospital	.01	.28

Table 11 cont.

C.JUNE:ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.28	.08	.24 (8,3)	.98

D.SEPTEMBER:ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.70	.49	2.1 (8,38)	.06

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.72	.64
Log ng/ml breast milk	-.77	-.69

Dependent Variables	Standardized Coefficients	Correlation with own variate
Jaundice	-.11	-.51
Birthweight	.64	.79
Gestational age	.36	.77
Days in hospital	-.41	-.39

birthweight. Some association of these exposure variables with longer hospital stays (.28) and lower gestational age (.26) was also seen.

No relationship between exposure and outcome variables was seen for the infants born in June (see Table 11C).

Canonical analysis of the data from babies born in September, exposed only during their first trimester, was near significance, $p = .06$ (see Table 11D). In the September group, prenatal heptachlor consumption and heptachlor level in breast milk loaded in opposite directions. Specifically, breast milk levels were associated with the undesirable outcomes, but prenatal heptachlor consumption was correlated with desirable outcomes, i.e., less jaundice and shorter hospital stays as well as higher birthweights and gestational age. In total, the analyses indicate that the relationship of heptachlor consumption with the cluster of dependent variables differed across birth months.

The consistent relationship of heptachlor level in breast milk with Cluster 1 perinatal variables indicates that ng/ml may be a useful measure of prenatal exposure. This is in accordance with the fact that level of a lipophilic contaminant in milk fat is essentially the same as the level in maternal adipose tissue (Jensen, 1983; Wolff, 1983). Organochlorines are transported from maternal fat to milk via blood and the pharmocokinetic properties of

the specific chemical determine blood/adipose and blood/milk ratios. Maternal plasma levels are determined by maternal body burden and themselves are related to prenatal exposure as well as breast milk levels (Wolff, 1983). While breast milk levels are essentially a postnatal variable, they also accurately reflect exposure during gestation, i.e., level of a toxic agent in maternal fat, and are associated with perinatal status of the infant. Their consistent loadings in these canonical correlation analyses would support this position.

Since infant or maternal blood and fat samples were not available, estimation of infant exposure was made from maternal report of consumption of contaminated milk and milk products for the period January-March, 1982. When this variable of exposure, heptachlor consumption, is considered across birth months, it also represents a specific level of exposure with a specific timing and duration. That is, infants born in March were exposed at a specific level throughout their entire gestation, the June babies were exposed for their first two trimesters and the September babies were only exposed at a specific level for their first trimester. The results of the canonical analyses then point to the conclusion that when heptachlor consumption continued through three trimesters, it was associated with a cluster of undesirable perinatal outcomes. No relationship was seen between consumption for the first two trimesters and the

perinatal variables of birthweight, jaundice, gestational age and length of initial hospital stay. However, consumption limited to the first trimester was associated with this constellation of variables in a positive direction.

This initially puzzling result seen in the September group may be more reasonable when it is recalled that the toxic agent is carried in a healthy medium. While the variable heptachlor consumption per day is considered here to represent exposure to heptachlor, it also reflects milk fat consumption per day or, by extension, nutrition of the mother. Therefore, for the September group, the positive, but non-significant, association suggested by a p value of .06 of the consumption variable with the desirable outcomes of less jaundice, shorter hospital stay, higher birthweight and gestational age then would be comprehensible as the results of better nutrition. Concomitantly, the continued association of ng/ml with the undesirable direction of outcomes reflects the effects of prenatal exposure to heptachlor.

The configuration of results suggests that exposure to heptachlor through three trimesters was associated with a constellation of perinatal outcomes of lower birthweight, lower gestational age, higher rates of jaundice and longer initial hospital stays. Furthermore, higher levels of prenatal exposure as reflected by levels of heptachlor in

breast milk were also associated with this same constellation of perinatal outcomes regardless of the timing and duration of prenatal exposure.

Within this study two jaundice variables were recorded from hospital records: presence or absence of a notation of jaundice and highest bilirubin level. The clinical diagnosis of jaundice indicated by yellow color of the skin, schlerae and mucous membranes (Miller & Keane, 1983) does not reliably predict serum bilirubin levels although reported jaundice is a clinical indication of hyperbilirubinemia (Hardy, Drage & Jackson, 1979). Of the 45 neonates diagnosed as jaundiced (37.5 % of the total sample of infants) bilirubin levels were available for 38. Number of cases and mean bilirubin levels for the total sample and for the separate birth months are presented in Table 6.

While some relationships between jaundice and specific exposure variables were seen in the zero-order correlation matrix, no correlations suggested association between bilirubin levels and exposure variables. For this reason the variable jaundice was included in the canonical correlation analyses of Clusters 1 and 2 rather than the variable bilirubin level.

For interest, a canonical correlation was calculated for Cluster 1 substituting in place of jaundice a variable created to reflect the presence of jaundice severe enough to

warrant laboratory testing of blood to determine bilirubin levels, i.e. presence or absence of blood tests for bilirubin. A canonical correlation of .42 (p=.057) was found with the pattern of loadings identical to that seen in Table 11A indicating that the relationships held when an even more stringent criterion of jaundice was used. A third set of canonical correlations was calculated substituting bilirubin level for reported jaundice in the Cluster 1 set of variables. A canonical correlation of .62 was found with the pattern of loadings nearly identical to that seen in the preceeding two analyses. However, since only 38 infants had blood tests and, therefore, only 38 subjects were included in the analysis, the correlation was not significant, p=.70.

Cluster 2: Birthweight, head circumference and jaundice

A second cluster of variables was seen in the simple correlation matrix which differed slightly from the pattern of variables in Cluster 1. Lower birthweights and head circumference as well as higher rates of jaundice were associated with levels of heptachlor in samples of breast milk for the March group (see Table 12).

The canonical correlation for the total sample was not significant when heptachlor consumption and birth month were the only exposure variables. However, as may be seen in Table 13A, a canonical correlation of .35, p=.056, was found when heptachlor level in breast milk was included as an exposure variable. In this analysis only ng/ml loaded

Table 12

Zero-Order Correlation Matrix for Cluster 2 Variables

	Birthweight		Jaundice		Head Circumference	
Total	r	p	r	p	r	p
Log HE	.11	.23	.03	.77	.17	.07
Log ng/ml	-.23	.06	.31	.01	-.17	.16
March						
Log HE	-.08	.63	.31	.05	.10	.53
Log ng/ml	-.38	.08	.54	.01	-.47	.03
June						
Log HE	-.01	.97	.10	.54	.09	.59
Log ng/ml	-.09	.71	.04	.88	.06	.79
September						
Log HE	.40	.01	-.26	.10	.27	.08
Log ng/ml	-.19	.34	.23	.25	-.06	.77

Table 13

Canonical Correlation of Exposure Variables with Birthweight, Jaundice and Head Circumference

A.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.35	.12	1.9 (9,153)	.056

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	-.31	.01
Log ng/ml breast milk	1.06	.95
Birth month	-.18	-.02

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight	-.52	-.80
Jaundice	.57	.77
Head Circumference	-.23	-.65

B.MARCH: ALL SUBJECTS

Canonical correlation	R^2	F	p
.43	.19	2.8 (3,36)	.055

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	1.00	1.00

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight	-.70	-.18
Jaundice	.91	.72
Head Circumference	.91	.23

Table 13 cont.

C.MARCH: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.65	.43	2.8 (6,34)	.028

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.55	.87
Log ng/ml breast milk	.59	.89

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight	-.31	-.54
Jaundice	.88	.96
Head Circumference	.02	-.50

Table 13 cont.

D.SEPTEMBER: ALL SUBJECTS

Canonical correlation	R^2	F	p
.46	.21	3.2 (3,36)	.036

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	1.00	1.00
Dependent Variables	**Standardized Coefficients**	**Correlation with own variate**
Birthweight	.86	.87
Jaundice	-.50	-.58
Head Circumference	-.05	.60

E.SEPTEMBER: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.60	.36	1.9 (6,44)	.10

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.92	.78
Log ng/ml breast milk	-.64	-.44
Dependent Variables	**Standardized Coefficients**	**Correlation with own variate**
Birthweight	.95	.91
Jaundice	-.40	-.58
Head Circumference	-.21	.46

heavily (.95) and was associated with smaller birthweight and head circumference and higher rates of jaundice.

For the March cohort, both the analysis with and without ng/ml included as an exposure variable were significant as may be seen in Tables 13B and 13C. In the analysis with the single exposure variable heptachlor consumption, a correlation of .43 (p=.055) was found. Only jaundice loaded to any extent on the outcome canonical variate which was interpreted as indicating that prenatal heptachlor consumption was associated with higher rates of reported jaundice. When heptachlor level in breast milk was included in the correlation, R=.65 with p=.028. In this analysis both heptachlor consumption and heptachlor level in breast milk loaded strongly (r=.87 and .89, respectively) and were associated with lower birthweight, smaller head circumference and more reported jaundice (see Table 13C).

Again, no significant canonical correlations were found for these matrices of variables in the June sample of infants. This was true for analyses both with and without ng/ml included as an exposure variable.

For September infants, a significant correlation (R=.46, p=.036) was found between the variable prenatal heptachlor consumption and the outcome variables of birthweight, jaundice and head circumference with higher consumption associated with larger birthweight and head circumference and lower rates of reported jaundice (see

Table 13D). However, when the variable of heptachlor level in breast milk was included in the analysis, a non-significant correlation, p=.10, was found between the cluster of exposure variables of heptachlor consumed per day and heptachlor level in breast milk and the cluster of outcome variables (see Table 13E). The patterns of loadings, however, were similar to the patterns found with Cluster 1 variables. Heptachlor consumption and ng/ml loaded in opposite directions with higher levels of prenatal consumption associated with less reported jaundice, higher birthweights and larger head circumference while ng/ml was associated with the opposite and more undesirable outcome pattern.

The reasoning employed in explaining the results for the Cluster 1 variables would also apply to these results. For the total group an overall relationship was found between prenatal exposure as reflected by the level of heptachlor in breast milk and birthweight, head circumference and reported jaundice. More explicitly, with higher maternal adipose tissue levels of heptachlor (and thus higher levels of prenatal exposure) lower birthweights, smaller head circumferences and more jaundice were found. For the March group where duration of exposure was longest and exposure extended through the third trimester, both prenatal heptachlor consumption and level of heptachlor in breast milk were associated with this undesirable

constellation of results. No relationship between exposure and outcome was seen for the June babies exposed only through their first two trimesters. For the September infants, as with Cluster 1 variables, heptachlor consumption was associated with a desirable direction of results and prenatal exposure as reflected by ng/ml with the undesirable direction of outcome. Again, the analyses of the September group data suggested that for this short exposure of one trimester the variable of heptachlor consumption reflected the beneficial effects of nutrition. The nonbeneficial effects of heptachlor exposure as represented by the variable ng/ml reflected the amount of heptachlor to which the infant was exposed prenatally.

Because of the association found in Cluster 1 of gestational age with ng/ml, a second set of canonical correlations was calculated using percentile scores instead of direct measures of birthweight and head circumference in order to remove the effect of lower gestational age. This set of analyses addressed the question of whether the effect on birthweight and head circumference was due to the shorter period of gestation or whether these babies were smaller in relation to other babies of the same gestational age. That is, if birthweight and head circumference were expressed in units which removed the influence of gestational age, would the relationship of these variables with heptachlor exposure remain?

The results of this set of analyses may be found in Table 14A-14E. They seem to indicate that for the total group and the September infants the effect of heptachlor exposure on birthweight and head circumference is associated with gestational age. That is, the lower birthweight and head circumference seen in these infants resulted from being born at an earlier gestational age. On the other hand, for infants born in March the association of heptachlor consumption and heptachlor level in breast milk with size remained after transformation of birthweight and head circumference to percentile scores. These results indicated, in conjunction with the analysis of Cluster 1, that for babies exposed through three trimesters not only was length of gestation affected by exposure to heptachlor, but that these babies were small for their gestational age as well.

Cluster 3: Physical abnormalities, serious delivery complications and 5-minute Apgar scores

A distinctive configuration of correlations emerged in the zero-order correlation matrix for the infants born in June. As may be seen in Table 15, for this group lower Apgar scores at five minutes, more physical abnormalities and more serious delivery complications were associated with increased consumption of heptachlor during gestation. Canonical correlation analyses yielded no significant correlations between heptachlor exposure

Table 14

Canonical Correlation of Exposure Variables with Birthweight Percentile Level, Jaundice and Head Circumference Percentile Level

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.18	.03	.63 (6,230)	.70

B.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.33	.11	1.3 (9,153)	.23

C.MARCH: ALL SUBJECTS

Canonical correlation	R^2	F	p
.46	.21	3.2 (3,36)	.03

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	1.00	1.00

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight %ile	-.66	-.34
Jaundice	.92	.68
Head Circumference %ile	.75	.20

Table 14 cont.

D.MARCH: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.65	.42	2.7 (6,34)	.03

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.43	.81
Log ng/ml breast milk	.70	.93

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight %ile	-.12	-.44
Jaundice	.83	.96
Head Circumference	-.25	-.62

Table 14 cont.

E.SEPTEMBER: ALL SUBJECTS

Canonical correlation	R^2	F	p
.43	.18	2.7 (3,36)	.06

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	1.00	1.00

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight %ile	.65	.79
Jaundice	-.59	-.62
Head Circumference %ile	.20	.66

F.SEPTEMBER: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.52	.27	1.5 (6,44)	.22

Table 15

Zero-Order Correlation Matrix for Cluster 3 Variables

	Apgar 5		Total Serious Complications		Total Physical Anomalies	
Total	r	p	r	p	r	p
Log HE	-.10	.30	.16	.08	.03	.76
Log ng/ml	-.16	.19	.07	.54	.04	.77
March						
Log HE	-.10	.55	-.06	.72	-.12	.44
Log ng/ml	-.23	.30	.11	.64	-.13	.55
June						
Log HE	-.31	.05	.43	.005	.34	.03
Log ng/ml	-.32	.17	.06	.81	.27	.25
September						
Log HE	.18	.27	-.02	.92	.08	.62
Log ng/ml	-.11	.57	.08	.68	-.04	.83

variables and this matrix of outcome variables for the total sample or for infants born in March or September. However, as can be seen in Table 16, for the June infants a canonical correlation of .55 was found ($p = .004$) with lower Apgar scores and higher numbers of physical abnormalities and serious delivery complications associated with increased heptachlor consumption. The same pattern of outcome variables was seen when ng/ml was included as an independent variable. However, since heptachlor consumption loaded 1.00 on the canonical variable representing exposure in this second analysis, the analysis was, in essence, another canonical correlation between heptachlor consumption and the set of outcome variables.

The June mothers as a group consumed larger amounts of heptachlor per day prenatally (a mean consumption of .037 mg/day as opposed to .021 and .028 mg/day for the March and September mothers, respectively). June mothers accounted for 17 of the 30 mothers in the top quartile of heptachlor consumption as well. The finding of these physical and functional anomalies associated with this group may reflect heptachlor's effects at higher exposure levels.

These June infants were exposed through their second trimester while March infants were exposed throughout their entire gestation, i.e., these two groups differ in that the exposure of the June babies did not extend through the third trimester. The third trimester is a time when the fetus

Table 16

Canonical Correlation of Heptachlor Consumed per Day with the June Pattern of Outcome Variables:Apgar 5, Total Serious Delivery Complications and Total Physical Anomalies

JUNE: ALL SUBJECTS

Canonical correlation	R^2	F	p
.55	.31	5.3 (3,36)	.004

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	1.00	1.00

Dependent Variables	Standardized Coefficients	Correlation with own variate
Apgar 5	-.17	-.56
Total Serious Delivery Complications	.69	.78
Total Physical Anomalies	.60	.62

grows, both adding weight and increasing in size (Hytten, 1980; Willson & Carrington, 1979). In addition, this trimester is a time of rapid brain growth with brain changes reflected in increases in head circumference (Galler, 1984; Naeye, Blanc & Paul, 1973; Leviton, Gilles & Dooling, 1983; Stein & Susser, 1976). March babies who were exposed throughout this time of rapid weight gain and brain growth did have effects on birthweight and head circumference associated with heptachlor exposure. For June babies, although mean exposure was higher, no effects on birthweight and head circumference were associated with exposure to heptachlor. However, in this group with the highest exposure, a unique cluster of effects was seen, a group of effects that was not seen in either the March or September groups. When in the Cluster 1 and Cluster 2 analyses a negative pattern of effects is seen in March infants and a positive pattern of the same effects is seen in September babies, clear evidence exists for a duration/timing effect. No such pattern of effects or differences in effects are seen for Cluster 3 variables which only emerged in the group with the highest exposure. The presence of physical anomalies within Cluster 3 could suggest that the levels to which this group was exposed may be high enough that not only are functional and growth effects associated with exposure, but morphological anomalies as well.

Growth Variables

All growth data were converted to percentile range scores prior to any analysis. Table 17 shows the means and standard deviations of the percentile range scores at 3, 6, 9 and 12 months for weight, head circumference and length for each of the birth months. While all groups were at the 50th percentile or above at birth (refer back to Table 5), weight scores declined steadily over the first year while head circumference and length percentile range scores remained relatively constant.

Whitehead and Paul (1984) reported similar trends in growth data from breast-fed infants in the United Kingdom, Finland and the United States. They concluded that the nearly universal use of National Center for Health Statistics (NCHS) growth charts which were based on data from formula-fed infants is no longer appropriate for samples of infants who are primarily breast-fed. Unfortunately, until new growth charts are constructed using systematically collected growth data from breast-fed infants, the NCHS charts are the best available (Whitehead & Paul, 1984).

No pattern of zero-order correlations was apparent between birth month, prenatal heptachlor consumption, duration of breastfeeding or level of heptachlor in breast milk and growth measures at 3, 6, 9 or 12 months. Since canonical correlation analysis may sometimes reveal

Table 17

Weight, Head Circumference and Length
Percentile Range Scores at 3, 6, 9 and 12 Months

	MARCH		JUNE		SEPTEMBER		ALL	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
3 Month								
Weight	4.67	1.67	5.21	1.63	4.29	1.54	4.69	1.64
Head	4.72	1.41	4.56	1.74	4.15	1.65	4.46	1.61
Length	5.23	1.65	5.52	1.89	4.88	1.61	5.19	1.71
6 Month								
Weight	4.12	1.83	4.94	1.25	3.50	1.47	4.14	1.62
Head	4.08	1.55	4.54	1.92	4.05	1.43	4.21	1.61
Length	4.77	1.54	5.53	1.25	4.20	1.20	4.77	1.40
9 Month								
Weight	3.58	1.59	3.74	1.48	2.96	1.62	3.44	1.58
Head	4.32	1.13	4.32	1.73	4.14	1.68	4.26	1.50
Length	4.73	1.28	5.10	1.59	4.43	1.33	4.75	1.40
12 Month								
Weight	3.15	1.48	3.90	1.17	2.88	1.30	3.32	1.39
Head	4.32	1.55	4.44	1.73	3.81	1.72	4.21	1.67
Length	4.46	1.35	5.64	1.47	4.14	1.75	4.78	1.64

Percentile Range Scores

$0 < 5$ %ile
$5 \leqslant 1 < 10$ %ile
$10 \leqslant 2 < 25$ %ile
$25 \leqslant 3 < 50$ %ile
$50 \leqslant 4 < 75$ %ile
$75 \leqslant 5 < 90$ %ile
$90 \leqslant 6 < 95$ %ile
$95 \leqslant 7$

relationships between matrices of variables not apparent in zero-order correlations, canonical correlations were calculated between this set of exposure variables and growth measures at the specific ages of 3, 6, 9 and 12 months. Analyses were performed as well between exposure variables and the specific measures of weight percentile range, length percentile range and head circumference percentile range across ages. Only two statistically significant canonical correlations were found, both of which were understandable in the context of research literature, but not especially germane to the focus of this study.

Hospitalization and Serious Illness

The numbers of children with serious illnesses and hospitalizations during their first year may be seen in Table 18. Serious postnatal illnesses were those other than common colds, fevers and illness of childhood. Included in this category were illnesses such as asthma, pneumonia, viral meningitis, blood abnormalities, febrile seizures, etc. Hospitalization was required either for serious illness or to correct some congenital condition. Overall, 10 children had subsequent serious illnesses and 16 required hospitalization during their first year. These numbers were too low to justify use of canonical correlation analysis.

Table 18

Frequency of Subsequent Hospitalization and Serious Illness

	March	June	September	All
Subsequent Hospitalization	6	4	6	16
Serious Illness	4	2	4	10

Performance on Behavioral Tests

Brazelton Scale

The mean and standard deviation for each of the scoring clusters for the June and September groups of babies can be seen in Table 19. Because of the low inter-tester reliability no further analyses of these data were done.

Bayley Scales

Mean group scores by month are presented in Table 20 for the 4-, 8- and 12- month Bayley tests. The correlations of the MDI and PDI within a specific age and between separate ages for the total group as well as the separate months are displayed in Tables 21A, 21B, 21C, and 21D. These correlations are generally consonant with those reported in the literature (Bayley, 1949, 1969; McCall, 1979; Yang & Bell, 1975).

When zero-order correlations between the independent measures of exposure and Bayley MDI and PDI scores were examined, no patterns of relationship emerged in the data for the total sample or in the data from infants born in the months of March and June. However, a pattern of positive relationships was seen between heptachlor consumption and MDI and PDI for babies born in September, i.e., those with only first trimester exposure to heptachlor (see Table 22). As with the perinatal and growth data a series of canonical analyses were calculated in order to discover any

Table 19

Lester Scoring Clusters Scores for the Brazelton Neonatal Assessment Scale

	June		September	
	M	S.D.	M	S.D.
Orientation	5.57	1.29	4.95	1.21
Motor	5.17	.70	5.13	.72
Range of State	3.73	.84	3.94	.83
Regulation of State	4.90	1.44	4.69	.95
Autonomic Stability	6.83	.67	6.90	.71
Reflexes	1.45	1.54	2.60	2.25

Table 20

Bayley Scales of Infant Development Mental (MDI) and Motor (PDI) Scores at 4, 8 and 12 Months

4 Months

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
MDI	110.9	11.3	111.6	11.4	115.4	11.9	112.6	11.6
PDI	114.3	12.3	118.5	9.6	114.3	9.9	115.7	10.8

8 Months

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
MDI	121.1	16.3	121.7	15.1	114.3	9.9	123.2	14.5
PDI	115.9	10.9	119.7	15.4	132.1	14.3	122.5	15.2

12 Months

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
MDI	123.5	10.0	117.1	13.5	120.7	12.1	120.5	12.1
PDI	119.5	11.7	116.3	14.9	115.2	17.9	117.0	15.0

Table 21

Within and Between Age Correlations of MDI and PDI

A. Total

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
MDI 4		.224*	.282**	.637****	.459****	.323**
MDI 8			.257*	.076	.373****	.158
MDI 12				.217*	.042	.526****
PDI 4					.330***	.416****
PDI 8						.275**

B. March

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
MDI 4		-.099	.175	.661****	.238	.359*
MDI 8			.182	-.167	.266	.098
MDI 12				.109	.133	.348*
PDI 4					.361*	.480**
PDI 8						.412*

C. June

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
MDI 4		.379*	.263	.750****	.467**	.223
MDI 8			.249	.370*	.217	.085
MDI 12				.231	-.083	.613***
PDI 4					.551***	.208
PDI 8						.246

D. September

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
MDI 4		.458**	.453**	.621****	.597***	.436**
MDI 8			.490**	.287	.603****	.388*
MDI 12				.517**	.237	.555***
PDI 4					.338*	.602***
PDI 8						.413*

* p<.05
** p<.01
*** p<.001
**** p<.0001

Table 22

Zero-Order Correlations Matrix for Exposure Variables with MDI and PDI at 4, 8 and 12 Months

Total

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
Log HE	.10	.06	.08	.14	.11	.10
Log ng/ml	-.18	-.10	.07	-.09	-.20	.33**
Duration B'stfeeding	.07	.09	.14	.08	-.01	.00

March

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
Log HE	.05	.07	.08	-.08	.20	.17
Log ng/ml	-.04	-.23	-.09	-.08	-.01	.61**
Duration B'stfeeding	-.09	.10	.27	-.08	.20	-.12

June

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
Log HE	-.11	-.14	-.08	-.02	-.06	-.18
Log ng/ml	-.27	.06	-.06	-.01	-.22	.11**
Duration B'stfeeding	.11	.04	.17	.10	-.15	.13

September

	MDI 4	MDI 8	MDI 12	PDI 4	PDI 8	PDI 12
Log HE	.36*	.26	.38*	.44**	.15	.36*
Log ng/ml	-.24	-.12	.06	-.09	-.30	.30**
Duration B'stfeeding	.17	.08	-.07	.37*	-.15	-.03

* $p<.05$
** $p<.01$

theoretically meaningful relationships between exposure variables and behavioral development.

Cluster 1: MDI and PDI scores at 4, 8 and 12 months

A canonical correlation was calculated for the matrix of independent variables (heptachlor consumed per day, duration of breastfeeding and birth month) with the matrix consisting of MDI and PDI scores at 4, 8 and 12 months. A second analysis was also calculated including heptachlor level in breast milk (ng/ml) as one of the exposure variables (which then included only data from breast-fed infants). The results of these analyses can be seen in Tables 23A and 23B.

Results indicated that birth month was related to performance on the Bayley scales at certain ages. That is, longer prenatal exposure was associated with lower MDI and PDI scores at certain ages of testing. As can be seen in Table 23A, the correlation between the exposure variables of birth month, prenatal heptachlor consumption and duration of breastfeeding with Bayley scores at 4, 8, 12 months was significant ($p=.0015$) with month loading most heavily on its canonical variate ($r=1.00$). In addition, MDI at 4 and 8 months and PDI at 8 months were negatively correlated with their canonical variate. These loadings indicate that length and timing of prenatal exposure had a negative relationship with performance on the Bayley at those specific ages. The variable of heptachlor consumption per

Table 23

Canonical Correlation of Bayley Scores at 4, 8, and 12 Months with Exposure Variables

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.55	.30	2.4 (18,238)	.0015

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	-.01	-.09
Duration breastfeeding	-.05	.00
Birth month	1.00	1.00

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 4	-.10	-.28
MDI 8	-.09	-.43
MDI 12	-.04	.13
PDI 4	.27	.00
PDI 8	-.99	-.89
PDI 12	.36	.14

Table 23 cont.

B.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.73	.54	3.1 (24,165)	.0000

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	-.54	-.33
Duration breastfeeding	-.50	-.26
Log ng/ml breast milk	.71	.59
Birth month	.51	.53

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 4	-.38	-.68
MDI 8	-.10	-.27
MDI 12	-.31	-.17
PDI 4	-.25	-.48
PDI 8	-.59	-.61
PDI 12	.82	.22

day did not load to any extent on its variate nor did the variable of duration of breastfeeding.

When heptachlor level in breast milk was included as an exposure variable, the same general pattern was seen ($p<.0001$). This analysis may be found in Table 23B. Although loadings on variates differed from those in the preceding analysis, overall, longer prenatal exposure and higher levels of heptachlor in breast milk were associated with poorer performance on both mental and motor components of the Bayley at 4 and 8 months. Prenatal heptachlor consumption loaded in the opposite direction from breast milk heptachlor level and birth month although its contribution to the relationship was not as strong. This loading may reflect the contribution of nutrition which is confounded with heptachlor consumption within this variable.

When the analyses relating exposure with performance on the Bayley were calculated for the separate birth months, no significant canonical correlations were found for the March and June groups. For the September babies the canonical correlation with heptachlor consumption and duration breastfeeding as exposure variables was strong, but not significant ($R=.67$, $p=.07$). This analysis suggested a positive relationship of prenatal heptachlor consumption and duration of breastfeeding with MDI scores at 4, 8 and 12 months and for the PDI at 4 and 12 months. A summary of this analysis may be seen in Table 24A.

Table 24

Canonical Correlation of Bayley Scores at 4, 8, and 12 Months with Exposure Variables:September Sample

A.SEPTEMBER: ALL SUBJECTS

Canonical correlation	R^2	F	p
.67	.45	1.8 (12,46)	.07

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.59	.59
Duration breastfeeding	.81	.80

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 4	.47	.63
MDI 8	.33	.30
MDI 12	-.16	.49
PDI 4	.82	.84
PDI 8	-.71	-.04
PDI 12	-.12	.30

Table 24 cont.

B.SEPTEMBER:ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.81	.65	2.1 (18,50)	.02

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.61	.42
Duration breastfeeding	.82	.79
Log ng/ml breast milk	-.34	-.27

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 4	1.02	.92
MDI 8	.15	.43
MDI 12	.14	.55
PDI 4	.14	.80
PDI 8	-.36	.32
PDI 12	-.22	.35

Table 24B contains a summary of the canonical analysis involving only September breast-fed infants, i.e., when ng/ml was included as an exposure variable and, thus, excluding all infants without a sample of mother's milk. The canonical structure of this analysis revealed a strong positive relationship of heptachlor consumption (r=.42) and duration of breastfeeding (r=.79) with performance on both the mental and motor sections of the Bayley at 4, 8, and 12 months. A similar association of breastfeeding with behavioral development has been reported by Young, Buckely, Hamza and Mandarano (1982), Edwards and Grossman (1979) and Rogers (1978). A suggested inverse relationship of heptachlor level in breast milk with scores on the Bayley, although not strong (-.27) is consistent with the pattern of association of breast milk heptachlor levels with nondesirable direction of outcomes.

A second set of analyses was performed in which the variable of duration of breastfeeding was adjusted to reflect breastfeeding up to and including the age of testing; i.e., Bayley MDI and PDI 4 scores with exposure variables when duration of breastfeeding varied from 0 to 4 months, MDI and PDI 8 with duration of breastfeeding being truncated at 8 months and MDI and PDI 12 with duration of breastfeeding truncated at 12 months. For the total sample, the canonical correlation of Bayley scores at 4 months with exposure variables was not significant (see Table 25A).

Table 25

Canonical Correlation of Bayley Scores at 4 Months with Exposure Variables:Maximum Duration Breastfeeding of 4 Months

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.20	.04	1.3 (6,218)	.27

B.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.46	.21	2.0 (8,120)	.0551

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.44	.53
Duration breastfeeding	.65	.66
Log ng/ml breast milk	-.38	-.39
Birth month	-.46	-.41

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 4	1.09	.99
PDI 4	-.14	.60

However, when level of heptachlor in breast milk was included as an exposure variable, the canonical correlation was significant R=.46, p=.0551 and indicated that longer duration of prenatal exposure to heptachlor and higher levels of heptachlor in breast milk were associated with lower scores on the Bayley at 4 months. However, longer duration of breastfeeding (up to 4 months) and higher prenatal consumption of contaminated milk were associated with better performance on the Bayley at this age. As may be seen in Table 25B prenatal heptachlor consumption and duration of breastfeeding both loaded positively and birth month and heptachlor level in breast milk loaded negatively. MDI was correlated .99 with its canonical variate. PDI is known to correlate .64 with MDI within this group so the suppression seen may reflect the high intercorrelation of these two measures at this age.

When data from separate birth months were examined, only the canonical correlation for the total group of September infants was significant. Table 26 presents the results of this analysis. For the September infants exposed only during their first prenatal trimester, increased consumption of heptachlor as reflected by the milk questionnaire and longer duration breastfeeding were associated with better performance on both the mental and motor sections of the Bayley at 4 months.

Table 26

Canonical Correlation of Bayley Scores at 4 Months with Exposure Variables:Maximum Duration Breastfeeding of 4 Months

SEPTEMBER:ALL SUBJECTS

Canonical correlation	R^2	F	p
.50	.25	2.8 (4,66)	.035

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.75	.91
Duration breastfeeding	.44	.72

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 4	.13	.70
PDI 4	.91	.99

A strong negative association between duration of prenatal exposure and motor scores on the Bayley at 8 months was indicated by the canonical correlation analysis of exposure variables and Bayley performance by the total group, $R=.45$, $p<.001$ (see Table 27A). Within this analysis, birth month correlated .99 with its canonical variate and PDI 8 correlated 1.0 with its variate. These high loadings suggest that this relationship might be seen in an analysis involving only these two variables. A similar trend was found in the analysis which included level of heptachlor in breast milk (see Table 27B). Higher levels of heptachlor in breast milk as well as longer term prenatal exposure were associated with lower mental and motor scores on the Bayley at 8 months. The moderate loading of prenatal heptachlor consumption (.31) in a positive direction may be reflecting the effects of prenatal milk consumption. No significant canonical correlations were found when the data for the birth month cohorts were analyzed separately.

Analysis of the 12-month data yielded a significant canonical correlation only when data from all infants with breast milk samples were considered. As may be seen in Table 28, duration of breastfeeding loaded most strongly (.74) and longer duration was associated with higher mental and motor scores at 12 months. Birth month and prenatal consumption of heptachlor also loaded strongly within this

Table 27

Canonical Correlation of Bayley Scores at 8 Months with Exposure Variables:Maximum Duration Breastfeeding of 8 Months

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.45	.20	4.1 (6,200)	.0007

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.11	.24
Duration breastfeeding	-.05	-.03
Birth month	-.98	-.99

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 8	-.004	.37
PDI 8	1.00	1.00

Table 27 cont.

B.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.47	.22	2.0 (8,114)	.0521

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.23	.31
Duration breastfeeding	.29	.04
Log ng/ml breast milk	-.37	-.44
Birth month	-.87	-.87

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 8	.12	.47
PDI 8	.95	.99

Table 28

Canonical Correlation of Bayley Scores at 12 Months with Exposure Variables:Maximum Duration Breastfeeding of 12 Months

TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.45	.20	2.5 (8,102)	.018

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.61	.47
Duration breastfeeding	.71	.74
Log ng/ml breast milk	.05	.23
Birth month	.33	.51

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 12	.95	.99
PDI 12	.11	.49

analysis. While the positive contribution of prenatal consumption of milk fat (containing heptachlor) can be understood as reflecting the effects of prenatal nutrition, explanation of the strong loading of birth month must await subsequent analysis.

When separate birth month samples were considered, only the analysis of data for March breast-fed infants was significant. As seen in Table 29, a canonical correlation of .80 was found ($p=.01$) with higher levels of heptachlor in breast milk samples and shorter duration of breastfeeding associated with lower mental and higher motor scores at 12 months. The opposite loadings of MDI and PDI in this analysis require further analysis for explanation. The finding of a different association of breast milk heptachlor level and scores on the Kohen-Raz may indicate that this particular analysis is statistically significant but theoretically meaningless.

Overall, the complex of findings for Cluster 1 indicated that timing and duration of prenatal exposure were related to postnatal behavioral development with longer term exposure being detrimental to early development. Infants exposed for only one trimester (September infants), however, showed a pattern of results which seemed to indicate again, as with perinatal outcomes, that for this group of infants heptachlor consumption should be interpreted as reflecting prenatal nutrition. The relationship of level of heptachlor

Table 29

Canonical Correlation of Bayley Scores at 12 Months with Exposure Variables:Maximum Duration Breastfeeding of 12 Months

MARCH: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.80	.64	3.4 (6,24)	.01

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	-.88	-.20
Duration breastfeeding	-.17	-.39
Log ng/ml breast milk	1.14	.66

Dependent Variables	Standardized Coefficients	Correlation with own variate
MDI 12	-.56	-.62
PDI 12	.79	.83

in breast milk to behavioral outcome measures was predominantly negative. Again, this was the same pattern of relationship seen with perinatal variables. The positive relationship of prenatal consumption of heptachlor (milk fat) at 12 months suggests that perhaps the detrimental effects of prenatal exposure are no longer present.

Cluster 2: Kohen-Raz scores at 4, 8, and 12 months

The Kohen-Raz scales essentially represent a breaking down of the global MDI score into its component behavioral parts. The five scales are eye-hand, manipulation, object relation, imitation-comprehension and vocalization-social contact. Eye-hand and manipulation are considered to be perceptual-motor scales. Object relation contains items such as "pulls string to recover ring" and "unwraps cube" and is considered to reflect behaviors critical to the development of sensori-motor intelligence. Imitation-comprehension and vocalization-social contact items measure nonverbal social contact behaviors as well as language development (Kohen-Raz, 1967).

The means and standard deviations of these scales for the total subject sample as well as for separate months are presented in Table 30. Score on any particular scale represents the number of items passed on that scale. At four months children usually have zero scores on imitation-comprehension and vocalization-social contact. By eight months, however, infants begin to pass items of both

Table 30

Kohen-Raz Scales of the Bayley Mental Scale at 4, 8 and 12 Months: Raw Scores

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
4 Months								
Eye-Hand	3.95	1.93	4.27	1.47	5.14	2.0	4.44	1.87
Manipulation	3.40	1.60	4.22	1.13	4.68	1.0	4.08	1.38
Object-Relation	.35	.58	.41	.60	.89	.88	.54	.73
Imitation	0	0	0	0	0	0	0	0
Vocalization	.03	.16	0	0	.05	.33	.03	.21
8 Months								
Eye-Hand	10.43	1.14	10.24	1.03	10.59	.89	10.42	1.03
Manipulation	8.30	.97	8.36	.78	8.21	.64	8.29	.81
Object-Relation	6.46	1.26	6.97	.92	6.26	.75	6.56	1.04
Imitation	3.73	1.37	4.55	1.75	5.24	.85	4.49	1.49
Vocalization	2.32	1.16	2.79	.74	2.44	.70	2.51	.91
12 Months								
Eye-Hand	14.31	1.60	14.03	1.78	14.48	1.54	14.28	1.63
Manipulation	8.84	.88	8.90	.40	8.97	.17	8.90	.56
Object-Relation	8.72	.99	8.81	.48	8.84	.44	8.79	.67
Imitation	7.53	.95	6.87	1.31	6.91	.88	7.10	1.09
Vocalization	6.31	1.28	6.03	1.02	6.24	.90	6.20	1.07

these more advanced scales which contain items with age placements of 8.4 to 26.0 months (imitation) and 7.0 to 19.1 months (vocalization).

These scales were used in an attempt to ascertain the relation of heptachlor exposure to the development of specific behavior skills. Preliminary analysis of raw scores suggested that at 4 and 8 months longer term prenatal exposure had a detrimental effect on emerging behaviors with a different pattern seen in the 12-month data where exposure variables (heptachlor exposure, duration of breast feeding and birth month) were positively related to the scales reflecting behaviors emerging at that age, i.e., imitation and vocalization.

In developmental tests, however, raws scores are commonly adjusted for age at testing. For example, in the Bayley Scales, age appropriate norms are used to convert raw scores to the standard scores of MDI and PDI. For the Kohen-Raz scales, adjustment for age was made by converting individual infant's raw score for each scale (number of items passed) into two separate scores: 1) percentage of age appropriate items passed using Kohen-Raz's assignment of age placement and 2) number of additional items passed. The mean percentage age appropriate score for each birth month cohort on each scale is presented in Table 31. The mean number of additional items passed is presented in Table 32. Separate canonical correlations were calculated for

Table 31

Kohen-Raz Scales of the Bayley Mental Scale at 4, 8 and 12 Months: % of Age Appropriate Items Scores

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
4 Months								
Eye-Hand	.833	.232	.910	.168	.875	.199	.872	.203
Manipulation	.715	.329	.892	.200	.931	.161	.843	.260
Object-Relation	0	0	0	0	0	0	0	0
Imitation	0	0	0	0	0	0	0	0
Vocalization	0	0	0	0	0	0	0	0
8 Months								
Eye-Hand	.954	.051	.958	.050	.968	.047	.960	.049
Manipulation	.981	.050	.991	.035	.979	.051	.984	.046
Object-Relation	.957	.117	.975	.061	.964	.083	.965	.091
Imitation	.714	.469	.846	.368	1.00	0	.833	.377
Vocalization	.757	.130	.914	.177	.809	.236	.824	.244
12 Months								
Eye-Hand	.979	.118	.992	.033	.995	.020	.989	.071
Manipulation	.983	.098	.989	.044	.997	.019	.990	.063
Object-Relation	.969	.119	.988	.038	.992	.030	.983	.074
Imitation	.979	.070	.957	.136	.990	.040	.976	.090
Vocalization	.943	.130	.964	.087	.963	.084	.956	.102

Table 32

Kohen-Raz Scales of the Bayley Mental Scale at 4, 8 and 12 Months: Additional Item Scores

	March		June		September		All	
	M	S.D.	M	S.D.	M	S.D.	M	S.D.
4 Months								
Eye-Hand	1.65	1.33	1.32	1.16	2.08	1.48	1.68	1.35
Manipulation	.78	.86	.57	.60	.68	.58	.68	.70
Object-Relation	.35	.58	.41	.60	.87	.82	.54	.71
Imitation	0	0	0	0	0	0	0	0
Vocalization	.03	.16	0	0	.05	.33	.03	.21
8 Months								
Eye-Hand	.89	.97	.67	.74	.91	.79	.83	.84
Manipulation	1.68	.71	1.48	.71	1.59	.56	1.59	.66
Object-Relation	1.49	.84	1.39	.75	1.27	.79	1.39	.79
Imitation	3.46	1.17	3.88	1.43	5.00	.89	4.10	1.34
Vocalization	.60	.72	.27	.52	.62	.49	.50	.62
12 Months								
Eye-Hand	3.13	1.04	2.68	1.62	3.15	1.50	2.99	1.41
Manipulation	0	0	0	0	0	0	0	0
Object-Relation	.94	.25	.68	.48	.76	.44	.79	.41
Imitation	1.66	.750	1.13	.72	.97	.77	1.25	.80
Vocalization	1.16	.92	.94	.85	1.06	.90	1.05	.89

percentage and additional scores at each age of testing. Within each analysis, the appropriate truncated duration of breastfeeding was used.

At four months the canonical correlation of exposure variables with percentage scores was significant for the total group R=.38, p=.008. As may be seen in Table 33A, birth month loaded most heavily (.94) although duration of breastfeeding also loaded to some degree (r=.35). The canonical structure indicates that a lower percentage of age appropriate items on the manipulation scale was passed by infants with longer duration prenatal exposure to heptachlor. It should be noted that there were no items with an age placement at or below 4 months on the object-relations, imitation or vocalization scales.

A similar pattern of effects emerged in the data when level of heptachlor in breast milk was included in the analysis (see Table 33B). Again, longer duration of prenatal exposure was associated with a lower percentage of age appropriate manipulation items passed. Heptachlor level in breast milk was also negatively related to percentage of manipulation scale items passed.

No pattern of relationship was found between exposure variables and percentage of age appropriate items passed on the Kohen-Raz scales at 8 and at 12 months when data for all three birth month cohorts were considered together. That is, an association between exposure to heptachlor and

Table 33

Canonical Correlation of % Age Appropriate Items Passed at 4 Months with Exposure Variables

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.38	.14	3.0 (6,218)	.0078

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.06	-.06
Duration breastfeeding	.35	.35
Birth month	.94	.94

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	.32	-.20
Manipulation	-1.11	-.96

Table 33 cont.

B.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.38	.14	2.1 (8,120)	.04

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.10	.24
Duration breastfeeding	.23	.05
Log ng/ml breast milk	-.34	-.41
Birth month	-.92	-.90

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	.03	.51
Manipulation	.99	.99

achievement of age appropriate behavioral milestones was seen only at the earliest testing. This relationship was in an undesirable direction with duration of prenatal exposure and level of heptachlor in breast milk associated with passage of a lower percentage of age appropriate items on the manipulation scale. No significant canonical correlations were found when data from the separate birth months were analyzed.

Age placement of items on the Bayley was determined by the age at which 50% of the infants in the normative sample passed the specific item. Also of concern here were items with age placement beyond the actual chronological age of the infants, i.e., items which reflected newly emerging behaviors. To examine the relationship of heptachlor exposure to these additional items, canonical correlations were calculated for the additional scores at 4-, 8- and 12-months. A summary of the analyses for the 4-month data may be seen in Table 34, for the 8-month data in Table 35, and 12-month in Table 36.

For the total sample of infants the canonical correlations for the additional items of the Kohen-Raz scales with exposure variables were all statistically significant. The canonical correlation at 4 months was marginal, $R=.35$ with $p=.059$, at 8 months was .60, $p<.0001$, and at 12 months was .46, $p=.02$. At 4 and 8 months birth month was negatively related to the number of additional

Table 34

Canonical Correlation of Additional Items Passed at 4 Months with Exposure Variables

TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.35	.13	1.7 (12,283)	.0593

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.08	-.04
Duration breastfeeding	.18	.18
Birth month	.99	.98

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	-.25	-.35
Manipulation	.60	.29
Object relations	-.99	-.79
Imitation	.00	.00
Vocalization	.27	-.13

Table 35

Canonical Correlation of Additional Items Passed at 8 Months with Exposure Variables

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.60	.36	3.6 (15,265)	.0000

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.22	.34
Duration breastfeeding	.00	.01
Birth month	-.95	-.98

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	-.07	.01
Manipulation	-.47	-.06
Object relations	-.27	-.23
Imitation	1.11	.82
Vocalization	-.05	.01

Table 35 cont.

B.TOTAL: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.63	.39	2.0 (20,180)	.01

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.29	.52
Duration breastfeeding	.02	-.30
Log ng/ml breast milk	.15	.13
Birth month	-.90	-.93

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	.08	-.01
Manipulation	-.29	.07
Object relations	-.44	-.18
Imitation	1.14	.81
Vocalization	-.25	-.08

Table 35 cont.

C. SEPTEMBER:ALL SUBJECTS

Canonical correlation	R^2	F	p
.62	.38	2.3 (10,54)	.03

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.25	.46
Duration breastfeeding	.91	.97

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	.26	.29
Manipulation	.99	.81
Object relations	.08	.22
Imitation	-.40	-.01
Vocalization	.50	.20

Table 36

Canonical Correlation of Additional Items Passed at 12 Months with Exposure Variables

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.46	.21	2.1 (12,198)	.02

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.38	.29
Duration breastfeeding	.44	.37
Birth month	.87	.84

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	-.70	-.18
Manipulation	.00	.00
Object relations	.24	.28
Imitation	.87	.76
Vocalization	.42	.34

Table 36 cont.

B.MARCH: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.97	.94	2.9 (9,10)	.0586

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.49	.63
Duration breastfeeding	.91	.49
Log ng/ml breast milk	.62	.39

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	-1.04	-.19
Manipulation	.00	.00
Object relations	.00	.00
Imitation	1.03	.47
Vocalization	.40	.80

Table 36 cont.

C.SEPTEMBER:ALL SUBJECTS

Canonical correlation	R^2	F	p
.62	.39	2.5 (8,46)	.02

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.99	.97
Duration breastfeeding	-.26	-.16

Dependent Variables	Standardized Coefficients	Correlation with own variate
Eye-hand	.75	.90
Manipulation	.00	.00
Object relations	.19	.04
Imitation	.51	.73
Vocalization	-.12	.46

items passed suggesting a detrimental effect of longer term prenatal exposure. However, at 12 months all exposure variables (heptachlor exposure, duration of breast feeding and birth month) were positively related to three of the four scales reflecting emerging behaviors.

At the 4-month testing when the data for the total infant cohort was considered, birth month loaded .98 on its variate and was negatively associated with scores on the eye-hand and object-relation scales (see Table 34). (The age placement of items on the imitation and vocalization scales puts these scales beyond the behavioral range of most 4-month-olds.) These results in conjunction with the findings for the age appropriate items at 4 months indicate that longer term prenatal exposure to heptachlor negatively impacts on behavioral development at this early age.

When heptachlor level in breast milk was included as an exposure variable and, thus, only data from breast-fed infants were used in the analysis, the resulting canonical correlation was not significant. Likewise, analysis of data from the separate birth month cohorts did not yield any statistically significant results.

At 8 months infants began to pass items in the imitation scale. It is is apparent even by inspection of the mean additional scores, i.e., prior to canonical analysis, that scores on the imitation scale were negatively associated with duration of prenatal exposure to heptachlor.

As may be seen in Table 32, March infants passed an average of 3.5 additional items on the imitation scale, June infants passed an average of 3.9 items and September infants passed an average of 5.0 additional items. Structure of the canonical correlation for the total group indicated that birth month was the most strongly loaded of the exposure variables and that it was was inversely related to performance on the imitation scale (see Table 35A).

A similar pattern of effects was seen in the data for breast-fed infants at 8 months, i.e., negative effects being seen in the scale which reflected most strongly the newly emerging skills at that specific age, imitation. The summary of this analysis may be seen in Table 35B. For the breast-fed infants, imitation loaded most strongly on its variate (.81). Scores on this scale were negatively related to birth month which loaded (-.93) as well as to duration of breastfeeding (-.30). The variable prenatal heptachlor consumption also loaded strongly (.52) and was associated with better performance on the imitation scale. This loading may be reflecting the positive effects of prenatal milk consumption which it also represents.

The only significant canonical analysis of the data from the separate birth months was for the total September group of infants. In these infants both prenatal consumption of milk (heptachlor) and duration of breastfeeding were associated with better performance on the

manipulation and eye-hand scales (see Table 35C). These results are yet another example of the positive effects of milk consumption in this group.

At 12 months infants are able to pass items of the vocalization scale as well as imitation items and have passed the maximum age placement of items on the manipulation scale. For the total group birth month still provided the primary loading (r=.84) for the exposure variate although in the opposite direction to that seen before; that is, longer duration prenatal exposure was no longer associated with detrimental outcome. Duration of breastfeeding and prenatal consumption of heptachlor (milk) also correlated with their variate, r =.37 and r=.29, respectively. As may be seen in Table 36A, imitation and vocalization scale scores loaded most heavily. Again, the variable heptachlor consumption's positive association with the outcome scales may again reflect its representation of milk consumption.

Analysis of data from all infants with a breast milk sample did not yield a statistically significant result. However, when additional scale scores for separate birth months were analyzed, two canonical correlations were significant. Summaries of these analyses may be found in Tables 36B and 36C. While specific loadings varied, the analyses of the March breast-fed infants and the September total group of infants lead to similar conclusions: that at

12 months the detrimental effects of exposure to heptachlor are not seen.

While it has been suggested that in those instances when the variable prenatal heptachlor consumption correlated positively with performance that this association may actually reflect benefits of prenatal milk consumption, an alternate explanation is possible. It is probable that maternal prenatal consumption of milk also reflects postnatal milk consumption by the infants since mothers who considered milk good for prenatal development also would consider it good for postnatal development. Therefore, the emergence of a positive association of heptachlor consumption with performance at 12 months may reflect benefits of postnatal consumption of noncontaminated milk. The emergence of this factor may have been delayed until after 8 months since the mean duration of breast feeding was 7.5 months and, therefore, not until 12 months were the majority of infants consuming noncontaminated milk. If this were the case, differences between breast-fed and bottle-fed might be expected in Bayley performance at 4, 8 and 12 months. It can be seen in Table 37 that the mean scores for the two groups do not differ. However, since an association between breastfeeding and behavioral development has been reported (Edwards & Grossman, 1979; Rogers, 1978; Young et al., 1982), the lack of relationship between breastfeeding and development at 4 and 8 months may be due to the fact

Table 37

Mean Bayley MDI and PDI Scores at 4, 8, and 12 months for Breast- and Bottle-Fed Infants

	Breast-Fed	Bottle-Fed
4 Months		
MDI	112	114
PDI	116	115
8 Months		
MDI	123	127
PDI	122	124
12 Months		
MDI	120	122
PDI	117	117

that the majority of the sample was still consuming heptachlor through their mother's milk. Resolution of this question awaits further investigation.

Potential Confounding Variables

Some variables with possible confounding effects on developmental outcome were examined. These included socio-economic status, tobacco use, prenatal drug use, prenatal alcohol consumption, and seasonal variability.

Social class was examined first since it has been found to be related to fetal outcome (Hardy et al., 1979) and duration of breastfeeding (Houston, Howie, Smart, McArdle & McNeilly, 1983). Kopp and Krakow (1983) in a historical review of studies of developmental risk concluded that socioeconomic status was always found to be a factor related to ultimate developmental outcome. The relationship of SES to performance on infant tests is unclear. On one hand, Golden and Birns (1976) concluded that SES effects on intelligence do not emerge before 18 months. On the other hand, Lamb, Garn and Keating (1982) reported a significant correlation of Bayley PDI with SES at 8 months. However, because of the huge sample size ($n>32,000$), statistical significance was reached with very small correlations, the largest $r=.08$.

The relationship of SES to breast feeding depends on the country in which the mother resides. In developing countries higher social classes tend to bottle feed, whereas

in industrialized western countries the opposite trend is seen (Messer, 1984). In the United States there is an increasing trend to breast feed (American Academy of Pediatrics, 1978) and this trend is accelerated in Hawaii (see SMS Research, 1982). Not only do more women in Hawaii choose to breast feed, but mothers breast feed longer (see SMS Research, 1982; Wilson et al., 1980).

SES was found to correlate .20 (p=.03) with heptachlor consumption and -.26 (p=.01) with duration of breastfeeding. That is, more milk consumption was associated with lower social class and a longer duration of breastfeeding with higher social class. The relationship of duration of breastfeeding with SES was seen despite the larger percentage of women breastfeeding for a longer period. That is, although more women in Hawaii breastfeed, and more women within this group breastfed longer, the association of longer duration breast feeding with higher socioeconomic status is still seen.

Zero-order correlations were examined to determine if SES was related to outcome measures as well as consumption of heptachlor and duration of breastfeeding. Only one significant correlation was found between SES and outcome variables (see Table 38): birthweight percentile score (r=-.18, p=.05), i.e., higher birthweight percentile score associated with higher social class.

While SES did not correlate with any outcome measure

Table 38

Zero-Order Correlations of SES with Selected Variables

With	r
Log HE consumed/day	.20*
Duration Breastfeeding	-.26**
Log ng/ml sample 1	.07
Birthweight %ile score	-.18*
MDI 4	.00
MDI 8	.12
MDI 12	-.04
PDI 4	-.01
PDI 8	.02
PDI 12	.03

* $p<.05$
** $p<.01$

except birthweight percentile score, caution dictated examination of those canonical correlations where heptachlor consumption and duration of breastfeeding loaded heavily. Within the group of analyses for perinatal variables, no consistent pattern of relationships emerged which could be attributed to SES. For example, with Cluster 2, heptachlor consumption was associated in the negative direction with outcome for the March babies and positively with the same outcome variable set for the September babies (see Tables 13b and 13d). If SES were the important factor, it would seem reasonable to expect a similar relationship for both the March and September babies. Exposure at different periods during gestation to a toxic substance carried on a nutritious medium could be expected to result in different outcome patterns, as was found. Likewise, the growth variables showed no relationships with heptachlor consumption which could also be seen as the being attributable to SES. Positive relationships of heptachlor consumption and Bayley scores were seen consistently for the September group, but for March and June infants this was not seen. Again, the pattern of relationships of the variable heptachlor consumption with outcome variables is comprehensible when attributed to exposure to a toxic substance. The patterns are not consistent with predictions made on the basis of social class.

While SES was correlated with birthweight percentile

score for the total subject population, this relationship was not seen for the March cohort. However, it was only within the March group that birthweight percentile score was related to heptachlor consumption (see Table 14). Furthermore, although the association between SES and birthweight percentile score was significant, SES would account for less than 4% of the variance in birthweight percentile score for the total group and less than 1% of the variance seen in the March infants.

Duration of breastfeeding within this study represents extent of postnatal exposure to heptachlor. Whenever it loaded to any degree, it was usually associated with a positive direction of outcome, e.g. Bayley results for the September babies or 12 month Kohen-Raz scores. Positive benefits of breastfeeding are not unexpected (see Hoffman, 1980; Jelliffe & Jelliffe, 1978) and the association between duration of breastfeeding and SES is not unique to this study. In fact, the educational and child-rearing characteristics associated with higher SES are often cited as interacting with nutritional benefits of human breast milk to account for advantageous outcomes attributed to breastfeeding (Galler, Ricciuti, Crawford & Kucharski, 1984). Thus, the correlation of SES with duration of breastfeeding within this study does not invalidate any findings. Rather, it would tend to validate the representativeness of the subject population.

Correlations of other possible confounding variables with heptachlor consumption and outcome variables were also examined. Tobacco use during pregnancy was reported by 24 of the 120 mothers with an average of 10.9 cigarettes smoked per day by the smoking mothers. Tobacco use was not correlated with heptachlor consumption or with heptachlor level in breast milk although Jensen (1983) reported that generally smoking mothers have higher levels of pesticides in their milk than do non-smoking mothers. While 13 of the 24 smoking mothers were in the June group, no correlation was seen between birth month and tobacco use. Duration of breastfeeding was associated negatively with tobacco use ($r=-.22$, $p=.03$) with smoking mothers breastfeeding for a shorter amount of time. This is not unexpected since both have been shown to be related to social class (Golub & Golub, 1981). Tobacco use was found to correlate with social class within this subject sample as well, $r=.24$, $p=.007$; i.e., higher SES mothers being less likely to smoke.

Despite the small numbers involved, several analyses were suggestive of effects of tobacco use by mothers. Overall, there was a zero-order correlation found between tobacco use and ponderal index ($r=-.17$, $p=.05$) with a similar, non-significant association seen between birthweight and smoking, $r=-.16$, $p=.07$. These correlations indicated that mothers who smoked tended to have thinner babies than mothers who did not smoke. This is congruent

with other research literature (see Hardy et al., 1979). When analyses involving physiological variables (e.g., jaundice, head circumference, etc.) and heptachlor exposure variables were examined, no relationships were seen which would be explained by tobacco use.

Since both heptachlor and smoking are known to induce microsomal enzymes (Timbrell, 1982), canonical correlations were calculated taking into account the relationship of heptachlor consumed and smoking with birthweight, length, gestational age and total delivery complications. Significant correlations were seen for the total group (R=.34, p=.055) and for the babies born in June (R=.59, p=.015). The correlations and the loadings can be seen in Tables 39A and 39B.

For the total sample, loadings on the canonical variables suggested that higher levels of heptachlor consumption and tobacco use were correlated with lower birthweights and gestational age and more delivery complications. Birth month also loaded -.52 on the canonical variate for the exposure variables. One problem in the use of canonical correlations is that mathematically derived canonical structures are not always theoretically meaningful (Tabachnick & Fidell, 1983). The loading of month within this analysis may be such an example.

The lack of effect on length combined with lower

Table 39

Canonical Correlation of Tobacco Use and Heptachlor Consumption with Birthweight, Length, Gestational Age and Total Delivery Complications

A.TOTAL: ALL SUBJECTS

Canonical correlation	R^2	F	p
.34	.12	1.8 (12,286)	.055

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.44	.54
Tobacco	.69	.72
Birth month	-.50	-.52

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight	-.83	-.33
Length	.94	.01
Gestational age	-.25	-.30
Total delivery complications	.84	.76

Table 39 cont.

B.JUNE: ALL SUBJECTS WITH BREAST MILK SAMPLES

Canonical correlation	R^2	F	p
.59	.35	2.6 (8,64)	.015

Canonical Structure

Independent Variables	Standardized Coefficients	Correlation with own variate
Log HE consumed/day	.25	.39
Tobacco	.93	.97

Dependent Variables	Standardized Coefficients	Correlation with own variate
Birthweight	-.54	-.61
Length	.20	-.43
Gestational age	-.42	-.63
Total Delivery Complications	.62	.80

birthweight was congruent with the overall simple correlation seen between tobacco use and ponderal index. Furthermore, the negative association of birthweight with tobacco use is consistent with the literature on effects of prenatal tobacco use (see Hardy et al., 1979; Meredith, 1975).

For the June infants with breast milk samples the effect was clear (p=.015), with tobacco use and heptachlor consumption associated with lower birthweight, shorter length, decreased gestational age and more delivery complications (see Table 39b). Since the June group not only had the highest level of consumption of heptachlor, but also contained 13 of the 24 smokers in the study, these results may reflect some sort of synergistic action.

Although research literature indicates that prenatal smoking by the mother may affect both short- and long-term postnatal behavior (Landesman-Dwyer & Emanuel, 1979; Landesman-Dwyer, Sackett & Meltzoff, 1983), no association of Bayley scores with maternal tobacco use was found. Therefore, conclusions drawn about association of duration of breast feeding with improved performance on behavioral tests within this study would not seem to be invalidated by the expected association of tobacco use with decreased duration of breast feeding.

All but four mothers reported taking drugs during pregnancy. However, drugs used were almost exclusively for

medical health purposes, i.e., prenatal vitamins, calcium and tylenol. The maximum number of drugs taken prenatally was 4 with the mean number of drugs of 1.8. No correlation was found between the number of drugs taken prenatally and heptachlor consumption, heptachlor level in breast milk, birth month or duration of breastfeeding.

Twenty-seven mothers reported prenatal alcohol use with a mean intake per week of 12.8 oz. Alcohol use did not correlate with heptachlor consumption, duration breast feeding or birth month. However,a significant negative correlation was found with heptachlor level in breast milk ($r=-.25$, $p=.04$). As shown in Table 40, alcohol use did correlate with several outcome measures, but in a direction opposite to that predicted by research literature, i.e., larger head circumference, longer gestation. These outcomes, however, were also associated somewhat with lower levels of heptachlor in breast milk. Whether alcohol consumption affects storage of heptachlor is an interesting question to be investigated in subsequent animal research. No significant correlations were found with Bayley scores. The associations found, while interesting, cannot be explained at this time and may be due to chance. In any event, they do not interfere with conclusions drawn about the main exposure variables of interest.

No racial/ethnic differences in milk consumption were found using the general linear model ($F=1.3$, $p=.26$). This

Table 40

Zero-Order Correlations of Prenatal Alcohol Use with Selected Variables

With	r
Log HE consumed/day	.01
Duration breastfeeding	.09
Log ng/ml sample 1	-.25*
Birthweight	.12
Head Circumference	.18*
Gestational Age	.22*
Jaundice	-.29***
Total Delivery Complications	-.16

* $p<.05$
** $p<.01$
*** $p<.001$

result is confirmed by Pfenninger et al. (1984) who found no differences among groups in a larger (n=400) sample of nursing mothers, 67 of whom also participated in this study. Mean milk consumption by the specific ethnic groups may be seen in Table 41. Birth month cohorts did not differ by racial/ethnic group membership, nor did level of heptachlor in breast milk vary by ethnic group. Ethnic differences in duration of breast feeding were found (F=.2.38, p=.04) with Caucasians breastfeeding longest; mean duration was 9.0 months. However, since no ethnic differences in performance on the Bayley were found, the effect of duration of breast feeding on Bayley and Kohen-Raz scores is probably not due to ethnic group membership.

Since within this study duration of prenatal exposure to heptachlor is confounded with month of birth, the issue of seasonal variability must be examined. Pasamanick and Knobloch (1966) in a retrospective epidemiological study reported that mental deficiency, complications of pregnancy and lower birthweight varied with season of birth. That is, they found that within their sample more mentally retarded children were born in the months of January, February and March, that more pregnancy complications were experienced by women who delivered in those months and that children born in the summer months tended to be significantly lighter. They attributed this cyclic phenomenon to the effects of the stress of heat on summer conceptions as well as to a

Table 41

Daily Heptachlor Consumption by Ethnic Group of Mother

	N	Mean mg/day	S.D.
Caucasian	54	.028	.023
Pacific Islander	2	.050	.054
Oriental	19	.024	.018
Filipino	7	.030	.018
Mixed with Caucasian	24	.029	.026
Mixed with no Caucasian	9	.018	.026
Other	2	.048	.003

hypothesized decrease in protein consumption by pregnant women in the hotter months.

While some studies have found a relationship between intelligence and season of birth (e.g., Diamond, 1981; Kanekar & Muckerjee, 1972; Martindale & Black, 1970), others have failed to find such a relationship (e.g., Concannon, 1968; Craddick, 1964; Roszkowski, 1980). Furthermore, Orme (1980) suggested that while seasonal variability is found in mental retardation with more mentally retarded born in the winter months, within the normal range of intelligence such seasonal variability is not seen.

Wharton and Karnes (1980) did not find the expected winter peak in births of mentally retarded children, but instead discovered that more children classified as learning disabled were born in the fall months. Diamond (1981; 1983) reported a similar association between fall births and classification of learning disability. This pattern is in opposition to the suggested seasonality of intelligence, i.e., both IQ scores and presence of learning disabilities having been shown to increase with month of birth. Both Diamond (1981; 1983) and DiPasquale, Moule and Flewelling (1980) attribute the seasonality of learning disability classification to cut-off date for school entrance. Younger children within a class, boys especially, are more likely to be referred for evaluation as learning disabled than children born earlier in the year.

The evidence for seasonal variability in intelligence is primarily from testing of older children. Salkind and Deaton (1978) who reported one of the only studies which observed differences in infant behavior associated with month of birth categorized the seasonal trend in their data as weak. It is interesting to note that an examination of some of the important books on infancy revealed that the topic of seasonal variability in infant behavior and development is completely ignored (See Hardy et al., 1979; Osofsky, 1979; or Mussen, 1970). This may reflect the status and perceived importance of this variable.

In contrast to the paucity of research on seasonal variation in behavioral development, seasonal variations in physical anomalies are reported more frequently. Although the relationship between season of birth and physical anomalies exists, these sequelae may be due to other factors which vary seasonally. For example, it has been possible to relate seasonal variations in defects to use of environmental chemicals. Theriault et al. (1983) suggested an association between exposure to vinyl chloride and birth defects, with the seasonal variation in birth defects in certain Ohio manufacturing towns accounted for by fluctuations in ambient vinyl chloride concentration. Lyon (1985) cited a study which reported an unusually high number of babies born with craniosynostosis in a community whose water was seasonally contaminated with runoff from mines.

In some areas cleft lip and palate are found to vary seasonally, but Gordon and Shy (1981) were able to relate cleft lip/palate to exposure to agricultural chemicals , rather than to season of birth.

These studies suggest that when birth or developmental outcomes vary seasonally, an effort should be made to determine what other potentially etiological factors exhibit seasonal fluctuation. Within the present study, perinatal variables such as Apgar scores or presence of physical anomalies were not related to time of conception or birth; that is, they did not show seasonal variation. However, developmental test scores at 4 and 8 months did vary with birth month. While birth month and extent of prenatal exposure cannot be separated within this study, a number of arguments can be made to counter the seasonal variability explanation of the findings: One, the results in the present study were found in infant testing and almost no seasonal fluctuation in behavioral test scores has been reported for this age range; Two, the scores within this study were within the normal range, and typically seasonal variability is found only at the ends of the distribution of scores; Three, there is no extreme variation in temperature or diet in Hawaii, a factor which was postulated by Pasamanick and Knobloch (1966) to account for their observations of seasonal variation. Moreover, the situation here is more analagous to Gordon and Shy (1981), Lyon (1985) and

Theriault et al. (1983) where exposure to a potential teratogen was found to fluctuate seasonally. In sum then, the results of the present study appear to be a function of variation in duration and timing of heptachlor exposure (i.e., birth month) rather than the result of seasonal variation.

Overview

The levels of heptachlor to which infants in this study were exposed were sufficiently low to predict that no serious effects on physical variables would be seen. However, the analyses of perinatal data indicated that: 1) long-term exposure, 2) higher levels of exposure extending through the first two trimesters of gestation, and 3) higher maternal levels of heptachlor as reflected by breast milk sample levels were all associated with disadvantageous perinatal outcomes. Specifically, for the total sample of infants with breast milk samples, higher levels of heptachlor in mothers' breast milk (a variable which reflected prenatal level of exposure) was associated with lower birthweight, lower gestational age, a higher rate of jaundice and longer initial hospital stay.

For babies born in March, and thus, exposed to heptachlor throughout their entire gestation, heptachlor consumption by the mother and heptachlor level in her breast milk both were associated with lower birthweight, smaller

head circumference, and higher rates of jaundice. The March babies were not only found to have lower birthweights, but these infants were also small in relation to their gestational age.

In the June cohort of infants, who were exposed to heptachlor through their first two trimesters, a relationship was seen between heptachlor consumption by their mothers and lower 5-minute Apgar scores, more serious delivery complications and more physical abnormalities. As a group these mothers had consumed more heptachlor per day than the March and June mothers, so these health effects at birth may reflect the effects of higher dose along with six months of prenatal exposure. Also within this group use of tobacco and heptachlor consumption were associated with lower birthweight, shorter length, lower gestational age and more delivery complications. This latter association may reflect a synergistic effect of heptachlor and tobacco on microsomal enzymes. A similar pattern of associations with tobacco use was seen in the analysis of data for the total sample.

A very different pattern of results was seen for the babies born in September whose exposure to heptachlor was limited to one trimester. For these infants the variable heptachlor consumption per day seemed to reflect the beneficial effects of the milk consumed by their mothers. That is, milk consumption was associated with less jaundice

and fewer days in the hospital as well as larger birthweight, head circumference and gestational age. However, prenatal exposure as reflected by heptachlor level in their mothers' milk, was associated with the opposite, and less desirable, pattern of results.

Postnatal growth did not seem to be adversely affected by exposure to heptachlor. The drop in weight percentile level from 3 to 12 months associated with both heptachlor consumption and duration of breastfeeding may be an artifact of use of the NCHS growth percentiles.

Research literature in teratology indicated that behavior might be affected even with low levels of exposure. The canonical correlation analyses of the behavioral data clearly showed: 1) lower Bayley scores at 4 and 8 months associated with longer term prenatal heptachlor exposure; 2) that exposure of a single trimester was not detrimental, and, in fact, consumption of milk and milk products by mothers of September babies was associated with better performance at most ages; 3) that exposure to heptachlor as reflected by the variable ng/ml usually correlated negatively with test performance; 4) that duration of breastfeeding occasionally worked in an opposing manner to the heptachlor which was carried in breast milk; that is, it was associated positively with developmental scores; 5) by 12 months the detrimental effect of longer term prenatal exposure was no longer apparent; and 6) that the detrimental

influence on mental development was most often reflected in those skills emerging at a specific age.

A duration/timing effect of exposure was seen in both the perinatal and behavioral data with the specific outcomes influenced by the medium on which the heptachlor was carried. Consistently, when negative effects were seen in the total sample of infants or in the March cohort, an opposite positive pattern of effects was seen in the September babies who were only exposed during their first trimester of gestation. Perhaps because the exposure to this toxic substance occurred through consumption of milk and milk products, "nature's most nearly perfect food", long term exposure resulted in detrimental outcomes and short term exposure was associated with positive outcomes. That is, when exposure extended through all three trimesters a detrimental effects was seen, but when exposure was only of three months duration, positive effects associated with consumption of the medium of exposure (milk) were seen. Although it may seem inconsistent to ascribe both detrimental and beneficial effects to the same exposure, the reality of the situation was that the more milk the mothers consumed, reflecting in most cases their concern for good nutrition, the more toxic substance they also ingested. Consequently, any measure of exposure to heptachlor also reflected maternal milk consumption.

The birth month cohorts of infants born in March, June

and September not only experienced different durations and timing of exposure to heptachlor, but also were exposed to different durations of non-contaminated milk. That is, mothers of the March infants potentially consumed no uncontaminated milk, while the June and September mothers consumed non-contaminated milk for one and two trimesters, respectively. With this perspective, the pattern of results is comprehensible.

The findings for the March group are congruent with predictions made from the principles of teratology, that effects would be most likely with longer duration exposures and that effects will vary with developmental stage during exposure. The last trimester of gestation is the time when the infant gains weight rapidly and brain growth accelerates resulting in larger head circumference; in the March group smaller head circumference and lower birthweights were associated with heptachlor exposure reflected by milk consumption and level of heptachlor in mother's breast milk. It has been suggested that the induction of microsomal enzymes by pesticides might lead to increased metabolism of estrogen so that levels might not be sufficient to sustain pregnancy; lower gestational ages were associated with exposure in this group. Heptachlor is known to have effects on the liver; in the total group and in the March cohort clinical jaundice was associated with prenatal exposure as reflected by heptachlor levels in breast milk. Exposure

during the third trimester when the brain is developing is thought to be most likely to produce behavioral effects; longer duration exposure was associated with lower scores on the Bayley Scales of Infant Development at 4 and 8 months.

For September infants whose mothers consumed contaminated milk only during the first trimester of pregnancy, milk (heptachlor) consumption was often significantly related to an opposite pattern of effects. The association of maternal nutrition and increased birthweight, head size and gestational age is supported by research literature (see Galler, 1984; Naeye et al., 1973; Stein & Susser, 1976; Winick, 1980). Within the September group, this same association was seen between milk consumption and outcome variables. That is, when heptachlor ingestion was of only three months duration, the expected positive relationship of weight, etc. with nutrition was seen. When heptachlor consumption extended throughout pregnancy, this relationship was not seen, i.e., in the March infants.

A similar reversal of outcome between infants with long term exposure as compared to infants with short term exposure was also found in the behavioral data. For the group as a whole, length of prenatal exposure was negatively associated with Bayley scores at certain ages. When the data for the September group was examined, not only were there zero-order correlations between Bayley scores and milk

fat (heptachlor) consumption, but a significant canonical correlation was found (R=.81, p=.02) in which heptachlor (milk) consumption and duration of breast feeding were positively related to Bayley mental and motor scores at all ages tested (4, 8 and 12 months). This finding is congruent with nutrition literature which has related prenatal nutritional status with subsequent postnatal behavioral performance (see Hicks, Landham & Takenaka, 1982; Pollitt & Thompson, 1977; Rush, 1984; Stein & Susser, 1976) although the subject sample here is at a higher nutritional level than has typically been studied, i.e., the present sample was not malnurished.

Dose effects were seen in two areas of the results: in the pattern of perinatal outcomes unique to the June cohort and in the constant association of the variable ng/ml with negative direction of results. The mothers within this study who gave birth in June consumed more heptachlor per day than did mothers who gave birth in March and September, i.e., .037 mg/day for June, .021 mg/day for March and .028 mg/day for September. In the June group lower Apgar scores at 5 minutes, more serious delivery complications and more physical abnormalities were associated with prenatal heptachlor consumption. This pattern of results was not found in any other exposure group. This finding may not represent a pure dose effect since these infants were exposed for their first two trimesters. Nonetheless, the

conclusion can be drawn that higher exposure levels for two trimesters are associated with this set of effects.

Since level of heptachlor in breast milk accurately reflects maternal prenatal body levels of heptachlor, the consistent relationship of this variable with disadvantageous direction of outcomes reflects a dose effect. That is, higher maternal levels of heptachlor were associated with the undesirable trend of results regardless of duration of prenatal exposure. Therefore, while consumption of contaminated milk may reflect one aspect of exposure to this toxin, the level of heptachlor in maternal breast milk may be a purer index of exposure, one unconfounded by the effects of nutrition. These findings concur with the contention of Eckenhausen, Bennett, Beynon and Elgar (1981) that the variable of primary concern in respect to organochlorines is the tissue concentration rather than the intake per day. Hayes (1975) in his classic texbook of toxicology of pesticides wrote that for any specific compound a direct relationship exists between storage and toxicity and that bio-magnification of a toxin up the food chain is the "quintessence of storage" (p. 167). Indeed, he asserted that when no relationship is found between concentration and a target effect, the target has been misidentified or analysis was faulty (p.167). In the pregnant woman fat is deposited in preparation for the energy needs of lactation (Winick, 1980) with the greatest

deposition occurring between the 10th and 30th week of gestation (Stein & Susser, 1976). For March mothers who consumed contaminated milk throughout their pregnancy, daily consumption and concentration in adipose tissue were significantly correlated and both were related to target effects. For June and September mothers who consumed both contaminated and non-contaminated milk, heptachlor intake was not related to target outcomes, but concentration in deposited adipose tissue as reflected by milk levels of heptachlor was.

By 12 months, the negative relationship between prenatal exposure and performance on the Bayley Scales was no longer apparent. Several alternate explanations can be proposed to account for the lack of effects at this age. One possible explanation is that the effects of a long period of prenatal exposure may diminish by 12 months thus, no longer providing the major loading. A second possible explanation is that since the mean duration of breastfeeding within this sample is 7.5 months, not until after 8 months are the majority of the infants being fed non-contaminated milk. Therefore, the depression of scores exists only as long as most of the infants are consuming contaminated milk.

A third explanation may be that a shift in the qualitative nature of infant intelligence occurs at around 8 months (McCall, 1976). McCall and his associates have suggested that correlations of 8-month tests with tests at

other ages is low because of a developmental stage boundary at approximately 8 months (McCall, 1979; McCall, Eichorn & Hogarty, 1977). Furthermore, analysis of the Bayley by McCall et al. (1977) found that principle components at 1-7 months differ from those found at 8 months. Based on these findings and the examination of the interage correlations of the Bayley, McCall (1979, 1982) proposed, in a Piagetian model, that the qualitative nature of intelligence changes at approximately 8 months.

It has been suggested that early infant development is strongly canalized, i.e., it follows a species-specific common developmental path (McCall, 1981; Scarr-Salapatek, 1976). During this early period the specific ontogeny of behavior seems to be genetically determined and variance from the normal sequence of emergence of behaviors is considered to be a criterion for abnormal development (Wolff, 1981). The behavior evaluated in infant tests essentally reflects neurological development (Connolly, 1981; Gesell & Amatruda, 1947; Prechtl, 1981) and these behaviors are highly canalized and prone to self-righting (Kopp & Krakow, 1983; McCall, 1979).

Kopp and Krakow (1983) concluded in a recent review of studies of biological risk in the infant that the sequence (but not timing) of development remains invariant despite biological stresses. It has been proposed that the variance seen in early infant test performance may be due to

biological factors such as nutrition and prenatal environment (Connolly, 1981; McCall, 1976). However, at around 12 months language and cognitive skills begin to emerge; skills which are more influenced by social and environmental factors than biological factors (McCall, 1976; McCall et al., 1977). Therefore, the biological factors which had influenced development up to this age may no longer be related to behaviors being evaluated by tests such as the Bayley.

The data from this study conform to this model. Early test performance was influenced by the biological insult of prenatal exposure to a neurotoxin, but effects were not seen in testing at 12 months. Furthermore, effects seemed to consist of temporary slowing of development at early ages, rather than permanent retardation. This disruption of the normal timing of behavioral emergence may account for the differences in inter- and intra-test correlations across the birth month cohorts seen in Table 21. As noted previously, these correlations are generally consistent with those found in the literature (Bayley, 1949; McCall, 1979; Yang & Bell, 1975). However, when the correlations for the separate birth months are compared, it can be seen that for the September infants 13 of the 15 tests are significantly correlated; while for the June and March infants only 6 of the 15 tests are significantly correlated. The mean correlation of all tests for the September group was .47;

for the June group the mean correlation was .32 and for the March group the mean correlation was .24. These differences in correlations may reflect yet another dimension of heptachlor's effect; i.e., its alteration of the normal timing of behavioral development results in disruption of the typical associations found between mental and motor development at a specific age as well as performance on this test at different ages.

Overall, the results seem to indicate that even low levels of exposure to heptachlor when of sufficient duration and/or at specific times during gestation were related to both physical and behavioral developmental outcome. These relationships were seen using both simple univariate correlation as well as multivariate analysis.

CONCLUSIONS

The present study has shown that subtle effects can result from low-level, long-term exposure to an environmental toxin. Since human data on such exposures are extremely rare, the results of this study are scientifically important. But, in addition, because this research does involve humans, the issue of the clinical importance of these findings must be addressed. That is, are these statistically significant results clinically significant?

While statistical significance holds regardless of the clinical significance of the results (Lester & Brazelton, 1984), some may doubt the importance of sub-clinical outcomes. In this study, no set of major deformities was consistently associated with the indices of exposure. Instead, clusters of subtle, but significant, effects were seen. These results fit the multiple effects model which proposes that when exposure to a toxin is low-level, a number of non-specific, often subtle effects will result, and that only at high dosages will a specific set of symptoms appear in exposed individuals. However, sub-clinical effects can be disadvantageous or adverse. The outcomes in this study although within the normal range would be classified as adverse using the criteria proposed by Chan et al. (1982): "physical, physiological, behavioral and biochemical changes that affect the general well-being,

growth, development or life span.." (p. 10). Additionally, it should not be overlooked that subtle or subclinical effects in some may be accompanied by more profound effects in the most sensitive (Fein et al., 1983). Germane to these results, as well, is the point made by Needleman et al. (1982) that a shift downward in the distribution of IQ (or developmental scores, or birthweight, etc.) results in more children functioning at lower levels and fewer at higher, more desirable levels.

Furthermore, as was discussed previously, the effects of toxins may have indirect effects on the child. For example, exposure to a toxin might result in irritability and impulsiveness in some children. In turn, agents of discipline (parents and teachers) may administer more or different types of aversive discipline to these children. Thus, a subtle effect of exposure to a toxin may be exacerbated as a function of contingency patterns. That is, a clinically non-significant result of toxic exposure may become significant due to the overlay of other factors. For all of these reasons, the fact that heptachlor exposure affected outcome within the normal range should not be interpreted to mean that these findings are of no practical importance.

Prechtl (1981, 1983) has advocated the use of the concept of optimality rather than normality. He argued that certain outcomes may be within the normal range, yet not

represent a most desirable or optimal result. A number of the findings of this study would be classified as normal, but not optimal. For example, in the March group the mean head circumference at birth was 34.5 cm which is within the normal range. Yet, head circumference at birth was negatively correlated with level of prenatal heptachlor exposure as reflected in breast milk samples ($r=.47$, $p=.03$), i.e., the higher the maternal level of heptachlor, the smaller the head circumference of the neonate. Thus, although the outcome itself was within the normal range, prenatal exposure to heptachlor did not optimize neonatal outcome. When such normal, but non-optimal, outcomes are associated with some sort of biological risk, concern is still warranted since these outcomes interact with environmental variables to determine future functioning.

However, the plasticity of development (Brazelton, 1983; Cohen & Parmelee, 1983; Prechtl, 1981) may result in the infants' overcoming any disadvantage imposed by the prenatal and lactational exposure to a toxin. Such plasticity is illustrated by the finding that while heptachlor exposure was related to developmental test scores at four and eight months, no relationship was found at twelve months. This finding also exemplifies what McCall (1983) referred to as the self-righting capabilities of the human infant and what Horowitz (1983) has called the invulnerability of the infant. This non-continuity of

development in certain instances has also resulted in the recognition of the importance of the effects of environmental factors such as mother-infant interactions and environmental stimulation in facilitating development beyond infancy (Cohen et al., in press; Cohen & Parmelee, 1983; Kopp, 1983; Sameroff & Chandler, 1975; Sigman et al., 1981).

While the infant's environment may be able to overcome or ameliorate less than optimal conditions, the same environment may have achieved a higher level of functioning absent the disadvantageous early factors. As Prechtl (1983) indicated, no dysfunction of the nervous system should be considered clinically unimportant. The results of the present study illustrate that low-level exposures to environmental contaminants cannot be assumed to be benign. With the optimal development of children at risk, the lack of data on harmful outcome can no longer be interpreted as evidence that an exposure is harmless.

Appendix A

Type and Frequency of Reported Maternal Illness During Pregnancy

Type	Frequency
Cold	39
Flu	22
Nausea	5
Headache	4
Asthma	4
Vaginal Bleeding	2
High Blood Pressure	1
Bronchitis	2
Collapsed Lung	1
Cough	2
Diabetes	2
Food Poisoning	1
Hemorrage	1
Herpes (non active)	3
Infection	10
Lupus	1
Seizures	1
Sinus Problems	1
Sore Throat	4
Spinal Virus	1
Teeth Problems	1
Pre-eclampsia	1
Toxemia	1
Premature Labor	1
Hyperthyroid	3
Hypothyroid	1

Appendix B

Preliminary Mother's Questionnaire

Preliminary Mother's Questionaire

1. Motner's name _____ I.D. # _____
2. Mailing address _____ English speaking yes no

   _____

   _____
3. Telephone # _____
4. Baby's name _____
5. Baby's Birthdate _____ M.R.# _____
6. Sex _____
7. Type of infant feeding _____
8. If breast feeding are you giving supplemental bottles? _____

   How many ounces of supplemental milk per day _____
9. How long do you plan to breast feed? _____
10. Amount of dairy products consumed per day (average during pregnancy)

		Brand
Fresh Whole Milk	_____	_____
2% Milk	_____	_____
Skim milk	_____	_____
Buttermilk	_____	_____
Evaporated milk	_____	_____
Imitation milk	_____	_____
Reconstituted milk	_____	_____
Powdered milk	_____	_____
Ice cream	_____	_____
Ice milk	_____	_____
Yoghurt	_____	_____
Cottage Cheese	_____	_____

Dishes Prepared with milk _____

puddings, pancake , cassaroles,etc. Estimate amount of milk contained in them

Appendix B cont.

11. Which group do you consider yourself as belonging to ?

Caucasian ____ Japanese ____ Chinese ____ Hawaiian _____

Filipino _____ Other Pacific _____ Other Asian _____

Mixed_____ Specify _____

12. Did you consume alcohol while you were pregnant? Yes No

If yes, how many oz. a day_____

Beer _____ Wine _____ Liquor _____

13. Did you smoke during this pregnancy? Yes No

How many cigarettes a day? _____

14. Did you take any drugs during pregnancy? Yes No

If yes, please list _____

_____

_____

15. Were you ill at any time during your pregnancy? Yes No

If yes, please describe and tentative dates of illness.

_____ _____

_____ _____

_____ _____

16. What was the last grade you completed in school?

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 Grad school

17. What was the last grade the baby's father completed in school?

o 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 Grad school

18. What is your occupation? _____

19. What is the baby's father's occupation? _____

Appendix C

Directions For Milk Collection

DIRECTIONS FOR MILK COLLECTION

PLEASE FOLLOW DIRECTIONS CAREFULLY

1. Use only the special bottles provided to collect the milk samples. Remove the lid carefully. The bottle cap has a thin teflon liner that can fall out. Do not touch the inside of the bottle or cap during collection.

2. Wash your hands with plain soap and water before nursing the baby. At each feeding be sure to nurse at least 2 minutes before collecting any sample of milk.

3. Remove the gauze from the wrapper, dampen with water and wipe the nipple area.

4. Hand Expression of Milk:

   You may collect breast milk from each breast 3 or more times a day. Support your breast with the last three fingers of one hand. Put your thumb at the upper rim of the brown ring (the aerola) and your index finger on the lower outside margin of the brown ring, about 1-1/2 inches back of the base of the nipple. Use gentle scissors-like motion against milk storage places inside the breast. DO NOT PULL DOWN or massage your breast. Don't slide the finger and thumb towards the nipple. Move your hand slightly back and forth in a circle so that you can express milk from all the sides and reach all the milk ducts (they radiate out from the nipple to all parts of the breast.)

   It is easier to collect the milk once the "let down" of the milk has started. When the baby has started to nurse on one side, it is easier to express the milk on the other side for this reason. If you collect between feedings, the milk will come more quickly and easily if you rub your nipple gently for a few minutes and cause a "let down." Do not use breast pump.

5. Place bottle in refrigerator between feedings. Add breast milk to the bottle at each feeding up to the the first mark on the bottle.

   When enough milk is collected, put the bottle in the freezer and call Jeanne at

Appendix D

Chart Review Form

Chart Review: Medical Records Number

1. Baby's name_____ I.D. No._____
2. Mother's name_____ M.R. #_____
3. Age of Mother_____ Para_____ Gravida_____
   Spontaneous Abortions_____
   Elective Abortions_____
4. Birthdate_____
5. Birthweight_____ Percentile_____
6. Apgar 1 min_____
   5 min_____
7. Type of delivery_____
8. Presentation other than vertex_____
9. Delivery complications Yes No
   Specify _____
   _____
   _____
10. Neonatal complications Yes No
    Specify diagnosis _____
    _____
    _____
11. Number of days spent in hospital_____
12. Physical anomalies _____
    _____
    _____

Appendix E

Instructions For Collecting Cord Blood For Organochlorine Pesticide Analysis

University of Hawaii at Manoa

Department of Psychology
2430 Campus Road • Honolulu, Hawaii 96822
Cable Address: UNIHAW

INSTRUCTIONS FOR COLLECTING CORD BLOOD FOR
ORGANOCHLORINE PESTICIDE RESIDUE ANALYSIS

1. The blood sample should be collected as soon as practical before clotting begins into a Green Top Tube. It generally is easiest to gently squeeze/ drip the blood from the cord and surrounding material into the tube. If the individuals prefers a large gauge needle needle may be used for collection. In both methods the action should be gentle so as to prevent the rupture of the red cells.

2. Approximately 10 ml whole blood should be collected. Lesser amounts should not be discarded. The laboratory will decide if sufficient sample is available for analysis.

3. Immediately after collection into the green top tube, the tube should be gently inverted two or three times and refrigerated. NOT FROZEN.

4. The blood sample should be properly labeled with name, date and time.

5. Samples will be picked up three times a week by Jeanne Hoffman. If additional pickups are necessary call her at 948-6677 or 395-5289. If any questions arise about collection of the cord blood call Dr. Lee Parks at 948-6677 or 955-5184.

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