

## Teratogenic Action of Carbaryl in Beagle Dogs

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Teratogenic Action of Carbaryl in Beagle Dogs. SMALLEY, H. E., CURTIS, JACK M., and EARL, F. L. (1968). *Toxicol. Appl. Pharmacol.* 13, 392-403. Carbaryl (1-naphthyl-*N*-methyl carbamate; Sevin), a reversible cholinesterase-inhibiting insecticide, was incorporated into the feed of pregnant beagle dogs and fed throughout the gestational period at levels of 50, 25, 12.5, 6.25, and 3.125 mg/kg body weight daily. Effects observed included an unexplained number of animals with dystocia (difficult births) due to atonic uterine musculature, an apparent contraceptive effect at the highest dose level, and a teratogenic action of carbaryl seen at all but the lowest dose level. The teratism was seen in 21 of a total of 181 pups born, or 11.6%. The characterization of the fetal abnormalities included abdominal-thoracic fissures with varying degrees of intestinal agenesis and displacement, varying degrees of brachygnathia, ecaudate pups, failure of skeletal formation, and superfluous phalanges. Several of the pups exhibited multiple defects that were difficult to categorize. It is concluded that carbaryl produces teratogenic and toxic effects in the pregnant beagle dog.

Carbaryl, or Sevin,<sup>2</sup> is a widely used broad-spectrum insecticide and has been classed as a reversible inhibitor of cholinesterase. Other interesting pharmacologic actions have been observed with carbaryl and other carbamate compounds. Georghiou (1965) reported that carbaryl caused a significant drop in the egg production of house flies and suggested that cholinesterase inhibition was not directly responsible for the reduction of fecundity. Amer (1965) found that carbaryl arrested mitosis in the root tip of *Allium cepa*; this action has also been observed with some carbamate and dithiocarbamate herbicides. Marliac (1964), Marliac *et al.* (1965), Ghadiri and Greenwood (1966), and Khera (1966) have studied the action of carbaryl in the chicken and duck embryo and report the presence of congenital deformities when the insecticide is applied directly to the embryo or injected into the yolk sac. Ghadiri *et al.* (1967) reported teratogenesis in chicks when carbaryl was fed to laying hens.

These observations aroused interest in whether or not this particular carbamate compound would affect the development of embryonic tissue in mammals, since published reports in this area are meager and variable. Robens (1968) reported that skeletal changes appeared in the guinea pig but not in hamsters after single large injections

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<sup>2</sup> Proprietary name for 1-naphthyl-*N*-methyl carbamate, generously provided by Union Carbide and Carbide, Inc.

of carbaryl. Thirty miniature swine (sows) were fed carbaryl in doses up to 30 mg/kg/day for the duration of pregnancy in our laboratory. There were no indications that carbaryl influenced reproduction in this species. This report presents the detailed observations of the effects of carbaryl on the reproductive processes of the dog.

#### MATERIALS AND METHODS

The beagle dogs used originated from the Food and Drug Administration colony located in Beltsville, Maryland, and were maintained under the administrative supervision of the Bureau of Veterinary Medicine. The breeding colony is a closed colony, and replacements usually come from the best of the litters produced. Therefore, some inbreeding is inevitable but brother-to-sister and father-to-daughter breeding is avoided; all pups transferred to the experimental stock are carefully examined for defects.

The animals were kept on concrete in individual pens with free access to outside runs except during periods of inclement weather and at the approach of parturition. Purina laboratory chow was fed throughout the experiment at the rate of 35 g/kg body weight daily and water was freely available. Extra feed was given toward the end of pregnancy and during lactation. Control females were housed and cared for under the same conditions as the test subjects. Basic sanitation was maintained. The occurrence of sexual heat or estrus was determined by observation, and the females in heat were mated on day 1. On day 3 the female was mated again to a different, unrelated male. The feeding of carbaryl-containing diets was started on the Wednesday following the second mating, which resulted in a variation of the starting date between day 3 and day 6 after the first mating. Whelping boxes as well as privacy panels were used during parturition.

Technical grade carbaryl (Lot 5072, 99.9% purity) was obtained from the manufacturer in powder form. The dosages of carbaryl for each test group were calculated, weighed, and incorporated in the diet by mechanical mixing. Diets were prepared once a week. Aliquots were removed from each batch for distribution sampling. Dosage of group I was 50 mg/kg/day. For each succeeding group, the dose was decreased by a factor of 2 until it reached the lowest dose of 3.125 mg/kg/day (Table 1). The experimental subjects were fed once daily and records of food intake were kept. The animals were observed at least daily and parturition was attended closely. Weekly weights were recorded for both the dam and the pups of each litter.

With the exception of 6 pregnant females used early in this experiment, all pregnancies were allowed to go to term unless dystocia developed; in these cases the dams were sacrificed and the pups were removed for examination. The 6 exceptions were dams that were delivered by hysterectomy 1 week before term to shorten the time required for this experimentation. However, the procedure gave us more difficulty than the time saved would justify, and information on viability and growth of the pups was lost.

After parturition, the dams and pups were carefully examined. Radiographs were taken of the pups if skeletal abnormalities were observed or suspected. Defective pups were dissected, and defects were characterized and recorded. In some cases, defects were discovered only after the pups had grown. All pups were autopsied at weaning

age. Those pups that were delivered normally were allowed to nurse until weaning at 8 weeks of age.

## RESULTS

### *General Observations*

Before the time of delivery, no recognizable signs of intoxication were observed in pregnant dogs fed carbaryl at any dose level. The average gestation period for all test animals which terminated in normal births was 62 days. The weight losses at parturition of all dose groups were similar to those of the control animals (Fig. 1). At necropsy

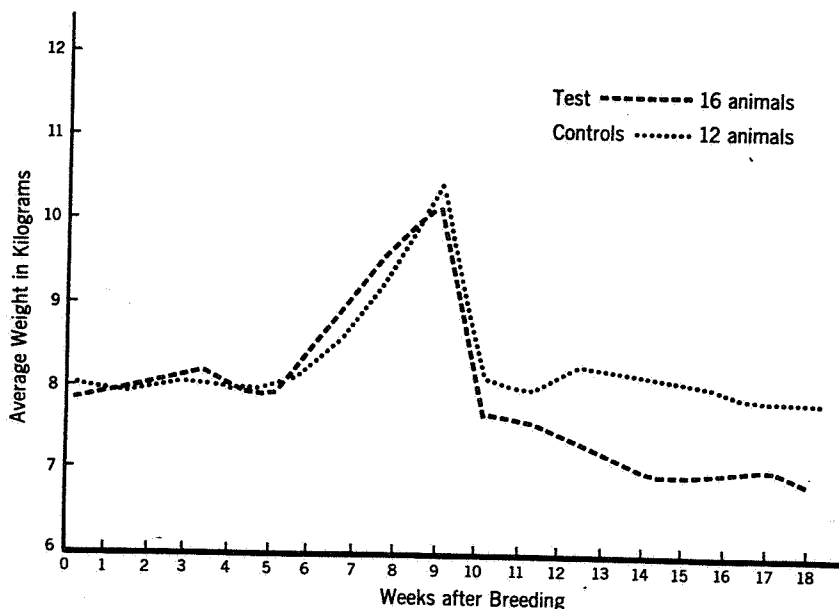


FIG. 1. Weights of test and control dams during gestation and lactation.

(8 weeks postpartum) the resorption and the implantation sites were quite evident, although small. The sex ratio of puppies born to the dams which were fed carbaryl was 54% males to 46% females. The ratio for controls was 49% male to 51% female. There was no difference between the sexes with regard to live births or neonatal deaths. The average birth weights of the puppies born to test females were essentially the same as the average birth weights of puppies born to control females; these averages included those litters in which there was a gross disparity in size and weights. In spite of the increased amount of food provided for all lactating females, the rate of gain of the test puppies was lower than that of control puppies (Fig. 2). The test puppies exhibited normal avid nursing behavior, but they tended to cry more than the puppies from control dams, and their mortality was higher than that of controls, especially in the higher dose groups (Table 1). Further study is required to characterize exactly the effect of carbaryl on lactation and to determine whether either the insecticide or its metabolic products contaminate the milk.

Puppy development proceeded normally. The eyes opened at 8–10 days, otic canals became patent in 6–8 days, and neurologic reactions were considered normal. Necropsy

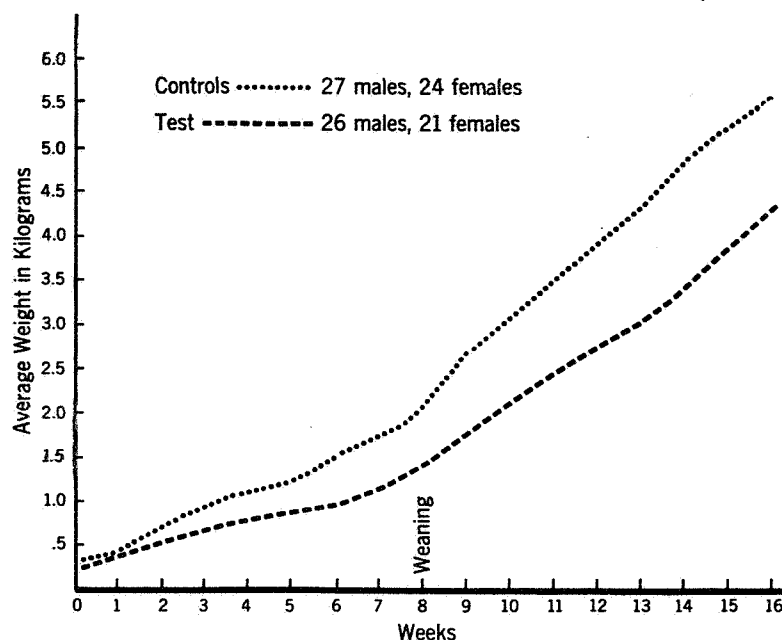


FIG. 2. Weekly weights of pups from birth through 16 weeks. Male and female pup weights have been averaged, as individual curves are essentially similar.

TABLE 1  
EFFECTS OF CARBARYL ON REPRODUCTION OF DOGS AND VIABILITY OF PUPS

Group	Dose (mg/kg body wt)	Number bred	Conception (%)	Number of dogs showing dystocia	Average number of pups in litter	Pups born alive (%)	Pups weaned (%)
I	50	8	37	3 <sup>a</sup>	3.5	0	0
II	25	9	78	3 <sup>a</sup>	3.8	60	39
III	12.5	18	89	5	4.8	38	23
IV	6.25	10	80	3 <sup>a</sup>	4.8	62	50
V	3.125	10	70	3	5.5	66	60
VI	0	16	81	0	5.4	81	73
VII <sup>b</sup>	0	390	80.25	15	5.6	86	82

<sup>a</sup> One female bred, conceived, but failed to deliver. On hysterectomy, only resorption sites were noted.

<sup>b</sup> Group VII data included for comparison are from records of the Food and Drug Administration Breeding Colony.

of puppies dying during the postnatal period did not reveal the cause of death, except in one instance of acute pulmonary inflammation which was not considered to be related to the experimental procedures.

*Parturition and Dystocias*

The effects of feeding carbaryl on reproduction in dogs and on the viability of the pups produced under these circumstances are presented in Table 1. Among the experimental animals an unusual number of difficult births was observed. The pattern may be described as delayed delivery accompanied by restlessness, anorexia, feverishness, and the presence of a green-black, foul-smelling discharge from the vagina. This symptomatology has been designated as dystocia. In each of 3 dams, 1 pup was delivered, then uterine contractions stopped and the dam was unable to deliver the rest of the litter. In a number of cases, pups of normal size had to be manually delivered from the birth canal. When this situation developed, parturition was terminated by euthanasia. An examination of the uterus showed that placental separation had occurred and that uterine musculature was atonic.

Three females, 1 from each of groups I, II, and IV, were bred and apparently conceived, but death of all fetuses occurred and fetal resorption was incomplete. The uteri in these cases showed four to six evenly spaced round prominences of the same size in each animal. On incision, it was found that the masses were encapsulated, closely adherent to the uterine mucosa, and composed of yellow-green caseous material with foci of calcification.

*Embryo Toxicity (Teratogenesis)*

A summary of observed data on the occurrence of embryo toxicity in dogs fed carbaryl is presented in Table 2. Of the total number of pregnant dogs fed carbaryl at various dosages, 21% produced puppies showing evidence of toxicity to the embryo. Disregarding fetal deaths and resorptions, a total of 21 puppies were abnormal; this is 11.6% of the puppies produced. The abnormalities usually were obvious on gross examination at birth but in a few cases, as noted in the detailed descriptions below, they were not apparent until the pups grew older.

TABLE 2  
EMBRYOTOXIC ACTIVITY OF CARBARYL IN DOGS

Group	Dose (mg/kg body wt.)	Number of litters	Number of pups	Resorp- tions	Litters with abnormalities		Pups with abnormalities	
					No.	%	No.	%
I	50	2	7	5	1	50	1	14
II	25	6	23	16	3	50	3	13
III	12.5	16	78	19	3	19	14	18
IV	6.25	7	34	33	1	14	3	9
V	3.125	7	39	22	0	0	0	0
VI	0	13	70	ND <sup>a</sup>	0	0	0	0
VII <sup>b</sup>	0	313	1753	ND <sup>a</sup>	3	0.9	3	0.1

<sup>a</sup> Not determined.

<sup>b</sup> Group VII data included for comparison are from records of the Food and Drug Administration Breeding Colony.

In group I (50 mg/kg), the ventral body wall of 1 of 3 pups delivered by hysterectomy had failed to close, leaving an oblong opening 4 cm by 2 cm through which the viscera had herniated. The fetal membranes covered the herniated viscera and the umbilical vein was quite prominent. The esophagus, cardiac portion of stomach, and rectum were patent even though stretched out of position.



FIG. 3. Litter of Dam 85D, group II (25 mg/kg). Disparity in size of affected pup is evident.

In group II (25 mg/kg), all 3 abnormal pups from the 3 affected litters were ecaudate. One pup's tail had seven coccygeal vertebrae terminating with an enlarged spinous process posteriorly; the other 2 pups had only 3 coccygeal vertebrae but these vertebrae were normal. One of these tailless pups showed extreme scoliosis, agenesis of external genitalia, failure of the right pubis and ischium to develop, an opening in the ventral body wall, and failure of the liver to develop to more than half size. This pup weighed only 166 g while its 2 littermates weighed 283 and 305 g, respectively. The forequarters, head, and forelimbs appeared to be normal, but from the abdominal fissure back the pup looked more like a frog than a pup. Figures 3 and 4 are photographs of this litter. The scoliosis revealed by X-ray (Fig. 5) shows extreme lateral deviation of the vertebral column with concomitant displacement of ribs and sternum. The pelvic bones were displaced due to the scoliosis, and the right pubis and ischium had not developed

normally. External genitalia were not evident but dissection showed presence of both uterus and ovaries. The anus was present but imperforate. The abdominal thoracic fissure extended from the umbilicus anteriorly to the sternum, 2.5 cm, but with no intestinal herniation. The intestines appeared normal; however, the stomach ballooned into the space where the right central and right lateral lobes of the liver would normally be found. The liver was formed normally, as far as having the required number of



FIG. 4. Ventral view of litter of 85D, group II (25 mg/kg), showing (arrow) abdominal fissure and position of hind legs.

lobes, but each lobe was greatly reduced in size. The gall bladder was buried within the parenchyma of the liver.

In group III (12.5 mg/kg), 6 pups in a litter of 9 had openings in the ventral body wall ranging from 1.5 cm to 4.0 cm in length at birth. Careful dissection and observation of the contents of the abdominal cavity showed visceral agenesis in varying degrees. Two of the pups were without grossly recognizable liver, pancreas, or intestines. The rudimentary esophagus was only about 4 mm long and ended just anterior to the thyroid glands. The anus was perforated for 3 mm only, with a thin strand of tissue extending anteriorly in the pelvis. Three other puppies had a normal visceral anatomy except for incomplete development of the liver; again the liver had normal lobe formation, but the size in all instances was less than half of normal. The umbilical cord was intact, and the fetal membranes covered the puppies. The urogenital system and adrenal glands in all pups were intact, but the kidneys appeared to be larger than normal.

Five of 6 pups in another litter at this same dose level showed extreme brachygnathia in which the lower incisor teeth were from 1.2 cm to 1.7 cm caudad to the upper incisors. The brachygnathia was somewhat apparent at birth, but became more pronounced as the puppies grew. Two of these 5 puppies had palpable hernias in the ventral midline anterior to the umbilicus; on necropsy 1 of these 2 pups had a persistent umbilical vein at 16 weeks of age.

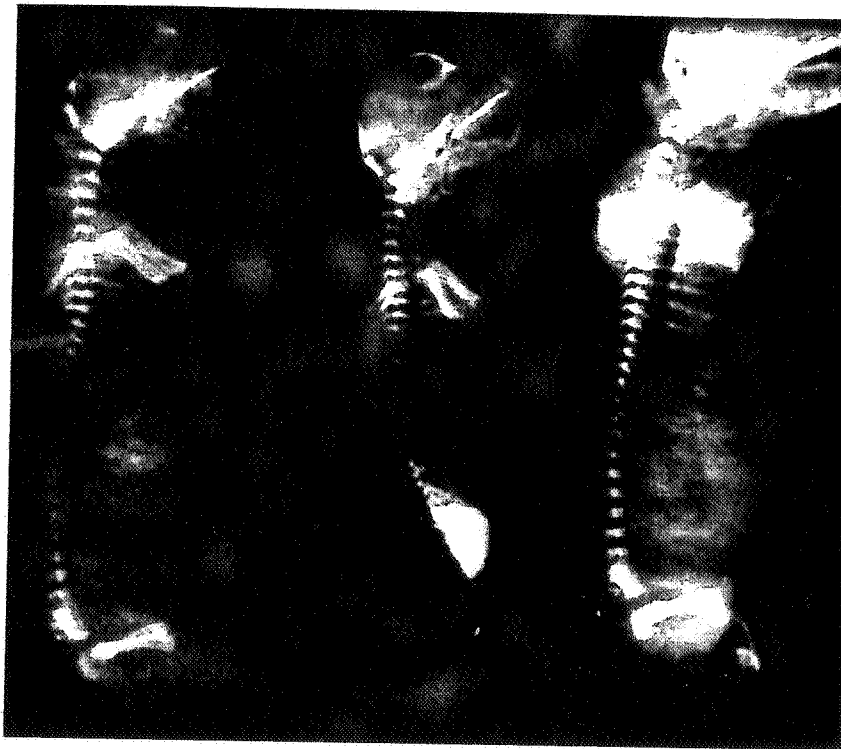


FIG. 5. Radiographic view of litter 85D, group II (25 mg/kg).

In the third litter affected, 3 of 5 pups showed lack of closure of the abdominal musculature at the linea alba anterior to the umbilicus through which the viscera were palpable, even though the skin covered the opening.

In group IV (6.25 mg/kg), of a litter of 4 pups, 1 pup was ecaudate at the 5th coccygeal vertebra and 2 others had superfluous phalanges on their hind legs. Of these last 2, 1 had a small (0.3 cm) opening in the ventral body wall which was not observed until necropsy.

#### DISCUSSION

The use of dogs to study the effect of a chemical on reproduction is somewhat unusual. One reason for this is economic, since the value of each individual animal is high, and the total expense for a study such as reported here becomes quite large. The length of gestation (62 days) makes studies relating to reproduction rather slow. The amount of information in the literature on reproduction and teratology in dogs is



meager when compared with the voluminous literature of such studies in rats and mice. Implantation in the dog is not accomplished until near the end of the first third of pregnancy; Gier (1950) lists day 18 as implantation and day 21 as completion of the amnion and starting placentation; Fox (1966) indicated that implantation occurs at 3 weeks post-conception, and that the zygote is nourished by "uterine milk" of the endometrium.

Seventy-one female beagles were used in this experiment. A large experimental colony must be on hand in order to have this many females available. From these 71 females, 51 litters were produced. Although the number of experimental dogs reported here is small as compared to similar studies with rats, the total number is relatively large, and the results reported are significant.

Partially resorbed fetuses were repeatedly observed in the uteri of carbaryl-fed dams; the incidence is recorded in Table 2. Similar control observations have not been made in the normal animal nor have such data been published, as far as we are aware. Although the incidence seems large, this condition cannot be attributed to carbaryl toxicity in the absence of a baseline.

The effects observed on reproduction are in three distinct categories and raise 3 questions:

1. Does the chemical under study interfere with conception? In our experiments the contraceptive action of carbaryl was apparent in group I only, which received 50 mg/kg/day, with no effect at lower doses. Further work is necessary to clarify the observation and to explain the mechanism of this effect.
2. Does carbaryl interfere with the birth process itself? Difficulties were observed with respect to the birth process that we have termed dystocia. The reasons for uterine atonia and the failure of the usual pattern of delivery are not completely known, but this interesting effect also deserves further study.
3. Is carbaryl a teratogenic agent? Interference with normal development of the fetus was observed at all dosages between 50 and 6.25 mg/kg/day. During the development of the data in Table 2, the 12.5-mg dosage seemed to be the most effective teratogenic dose, but this conclusion was proved to be untrue when the data were finally tabulated. Statistically there is no significant difference between the 9% of pups affected at 6.25 mg dosage and the 18% affected at 12.5 mg. In addition, the most serious effects were seen at 12.5 mg, namely, failure of development of the liver, but this defect did appear to a lesser extent at other doses. The value of 14% abnormalities at a dosage of 50 mg/kg is probably atypically high because of the small number of observations at this point; at this dosage the interference with conception or implantation appears, making it difficult to generate the number of observations desired. These data, although not extensive enough to be conclusive, suggest that the development of teratogenesis in the dog in response to carbaryl is not dose related.

This same phenomenon was equally difficult to understand from the point of view of litters affected. At 25 mg/kg, 3 of 6 litters were affected and at 12.5 mg/kg, 3 of 16 litters were affected, but the differences were still not statistically significant. In spite of these unsatisfactory aspects of the evidence presented and the insufficient observations in some areas, we concluded that carbaryl was teratogenic in the dog.

The teratogenic properties of several carbamates have previously been reported. Sinclair (1950) and Nishimura and Kuginuki (1958) showed that urethane (ethyl

carbamate) had a specific transplacental effect and induced congenital malformations in mice. Karnofsky *et al.* (1954) reported that the naturally occurring carbamate physostigmine caused terata in chick embryos. Howell (1964) injected diethyldithiocarbamate in rabbits intravenously and reported a decrease in serum copper levels and adverse effects in pregnancy characterized by fetal resorptions.

The normal incidence of malformations in beagle dogs has not been completely determined. Andersen (1957) reported that of 234 litters whelped over a 4-year period, there were 25 terata in 1157 pups born, an incidence of 2.1% congenital abnormalities. Six of these 25 were characterized as abdominal-thoracic fissures. Information made available to us from records of the Food and Drug administration breeding colony (group VII, Table 1) shows an incidence of 0.17% congenital abnormalities. The incidence of inherited defects is expected to increase as the ratio of inbreeding rises and may be explained on the basis of simple genetics. However, developmental defects often appear to result from interactions of environment and genetics—a potentiation, as it were, of a submerged fault. Kalter (1954) stated: "This may help explain why some malformations show an hereditary tendency but do not conform to the rules of simple Mendelian inheritance."

Abnormalities of the jaws and skull of the canine have previously been reported. Fox (1964) indicated that skull proportions are an inheritance function and that the upper jaw shape and mandibular shape are inherited independently of each other. The shape and proportions of the skull may not be obvious in the newborn, as in this instance, but become more obvious as the postnatal growth proceeds. A correlation between growth rate and degree of brachygnathia was seen in the pups cited; the pup with the most extreme brachygnathia weighed the least, and the normal pup weighed the most. Brachygnathia may interfere with milk intake and certainly interferes with solid food intake; caked food often had to be removed manually from the palate of the more extreme brachygnathous pups.

The midline defects seen as the dominant and most consistent malformation indicate a non-union or weakness of the linea alba. Fox (1963) stated that the direct cause of this abnormality may be an inherited factor affecting fibrosis and union of abdominal aponeurosis and that this disappeared at about the age of 12 weeks; he also reported that this was often seen in conjunction with inguinal hernias and 75% of the pups so affected were males. In contrast to his data, malformations in this study were not sex related, and no inguinal hernias were seen in any pup. Further, necropsy of several pups at 16 weeks of age revealed that the defect was palpable and still present.

Cannibalism in dogs is not prevalent but is not unknown; overeager removal of the umbilical cord may lead to ingestion of the intestines of the pup but this occurrence can be easily ascertained by examination of the dam's stomach and gut contents on necropsy soon after parturition. It is thought that cannibalism in carnivores may be due to any of several causes: perverse appetite, nutritional deficiencies, psychosis, fear, or perhaps the birth of defective young. Two pups of a test dam (at 12.5 mg/kg) were born apparently normal; the dam, however, continued licking the pups for several days until they were completely denuded of skin.

A temporary recession during the period of rapid growth of the fetus may lead to viable monsters. Different organs of the various systems may be affected by environmental factors acting at different periods of organogenesis. The lack of expressivity of

defects—that is, the several different types of defects seen—may well be due to the constant exposure of the embryo and fetus to carbaryl throughout gestation. Potter (1961) says that gross anomalies usually induced at an early embryonic stage are seen as minor defects at a later stage or at birth, if the defects are not lethal when induced. Similarly, such defects may be masked, inapparent, or insignificant until after birth and normal growth occurs, or they may be completely insignificant due to compatibility with life; these defects would not be observed, of course, except on occasion of necropsy.

The dosage of carbaryl at which the results reported here occur is worthy of some comment. In other studies that will be reported shortly on the toxicity of carbaryl to the adult animal, no clinical signs of toxic responses or biochemical changes that could be measured occurred below 125 mg/kg/day. None of the females that received carbaryl during the course of pregnancy showed any signs of toxicity prior to the time of delivery. The dosage (12.5 mg/kg/day) at which the production of teratology was first noted was one-tenth of the lowest dosage that produced frank toxic responses in the adult animal.

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