V. DEVELOPMENT OF A STANDARD

Basis for Previous Standards

In 1964, the American Conference of Governmental Industrial Hygienists (ACGIH) [146] proposed a tentative threshold limit value (TLV) for carbaryl of 5 mg/cu m of air. This was adopted as a recommended TLV by the ACGIH in 1966 [147] and has not been changed since then. The ACGIH limit for carbaryl continues to be 5 mg/cu m of air. [148]

According to the most recent (1971) ACGIH Documentation, [149] the TLV of 5 mg/cu m for carbaryl was recommended to provide a safety factor for protection against systemic effects. Cholinesterase inhibition was considered by the Threshold Limits Committee to be the basis of the toxic action of carbaryl; no other types of toxicity were mentioned. The TLV was based on the work of Best and Murray, [28] who indicated that 31 mg/cu m of carbaryl could be tolerated. However, the 31 mg/cu m was an average of only two air samples. Neither the duration of exposure nor the number of workers exposed at that concentration was specified by Best and Murray. [28] This exposure (31 mg/cu m) was calculated by the ACGIH to be equivalent to inhalation of 310 mg/man/day.

The documentation referred to the work of Carpenter et al, [27] who reported that airborne concentrations of 10 (5-20) mg/cu m of Sevin 85S produced neither mortality nor grossly visible injury in rats exposed 7 hours/day, 5 days/week, for 90 exposures. The ACGIH calculated that man in such an atmosphere would inhale about 100 mg of carbaryl a day.

Standards for carbaryl in foreign countries are those of the Federal Republic of Germany (5 mg/cu m as an 8-hour TWA) [150] and of the USSR (1

mg/cu m as a ceiling). [151] The basis of the USSR standard is inferred to represent a tenfold margin of safety derived from a threshold concentration obtained in long-term animal studies. [39] In addition, this concentration (1 mg/cu m) was stated as being somewhat below the concentration which caused a slight fall in cholinesterase activities of workers. [39]

The present United States federal standard for occupational exposure to carbaryl is an 8-hour TWA limit of 5 mg/cu m of air (29 CFR 1910.1000, published in the Federal Register 40:23072, May 28, 1975). This standard is based on the ACGIH TLV recommendation.

Basis for the Recommended Standard

The absorption of airborne carbaryl during workplace exposure is considered to be primarily through the routes of inhalation and dermal contact and, to a lesser extent, by ingestion. The airborne concentration at which carbaryl will induce some or no signs or symptoms of poisoning in humans has not been reported. The airborne concentrations of carbaryl present when 7 of 14 men engaged in hand-removal of carbaryl from a plugged storage bin became ill were not determined. [13 (sec 7)] Although these workers were supposedly wearing respirators, the protective devices were ineffective against inhalation of carbaryl dust. The complete recovery of the workers in less than 36 hours without medical intervention suggests a rapid reversibility of carbaryl intoxication once exposure is halted.

Best and Murray [28] reported that signs and symptoms of carbaryl intoxication were not detected among 59 workers exposed to airborne concentrations ranging from 0.03 to 40 mg/cu m. Workers exposed at high concentrations of carbaryl usually wore respirators, and those exposed at

lower concentrations did not routinely wear respirators. Significant inhibition of cholinesterase activity was not reported; however, the methods used were not adequately sensitive.

In a short-term inhalation-absorption study, [13 (sec 9,10)] two workers who wore either a respirator or skin protection equipment, but not both, were exposed to airborne carbaryl at a concentration of approximately 50 mg/cu m during 2 workdays. No apparent adverse effects were observed.

A report from Russia [39] involving agricultural workers' exposure to carbaryl indicated that exposure at 2 mg carbaryl/ cu m in the air, 4-6 hours/day, for 3-4 days produced some inhibition of cholinesterase activity (11-24%). However, clinical assessment showed no additional evidence of changes induced by cholinesterase inhibition. The method used for determining cholinesterase activity was not specified.

Several species of animals have been experimentally exposed to airborne carbaryl. [27,39] There were no deaths reported in guinea pigs exposed to carbaryl for 4 hours at concentrations of 230, 322, and 390 mg/cu m, but nasal and local ocular irritation were noted in those animals exposed at the highest concentration. [27] Signs of cholinesterase inhibition were noted in dogs within 5 hours of exposure to carbaryl at 75 mg/cu m. [27] Neither deaths nor carbaryl-associated lesions (C Carpenter, written communication, January 1976) were reported in rats exposed to carbaryl at an average concentration of 10 mg/cu m (5-20 mg/cu m) for 7 hours/day, 5 days/week, for 90 days. [27] Three groups of four cats each were exposed to carbaryl at 16, 40, and 63 mg/cu m, 6 hours/day, for varying periods up to 4 months. [39] At 16 mg/cu m, there were no signs of toxicity after 4 months' exposure; at 40 mg/cu m, there was a loss of

unspecified conditioned reflexes and a 50% decrease in erythrocyte cholinesterase activity during 2 months' exposure; at 63 mg/cu m, the cats exposed to carbaryl for one month showed periodic salivation, with 31-40% and 41-58% decreases in serum and erythrocyte cholinesterase activities, respectively. The author concluded that 16 mg/cu m was the threshold concentration for carbaryl in cats. If humans and lower animals do not differ signifcantly in their susceptibility to inhaled carbaryl, the results of inhalation studies in several animal species [27,39] would indicate that 16 mg/cu m can be considered the no-adverse-effect level with respect to toxic manifestations of cholinesterase inhibition in humans. This assumption is supported by the work of Best and Murray, [28] who noted no symptoms of carbaryl intoxication in humans exposed to the insecticide at airborne concentrations ranging from 0.03 to 40 mg/cu m. It is also not in conflict with the results of Yakim [39] who reported reductions in blood cholinesterase activity (measured by an unspecified method) following 4- to 6-hour exposures of workers to carbaryl at average airborne concentrations of 2-4 mg/cu m, since no clinical evidence of anticholinesterase activity was observed at these concentrations.

Few oral ingestion studies on the effects of carbaryl in humans have been found. A suicide attributed to the ingestion of an apparently large dose (possibly 400 g) of carbaryl was reported. [40] The significance of this report cannot be determined since the patient was treated with an oxime, a useful antidote for cholinesterase inhibition caused by organophosphates, but not useful in cases of carbaryl poisoning. [21]

Single oral doses of up to 2 mg/kg of carbaryl taken by male volunteers produced no signs or symptoms of intoxication. [32] A higher

single oral dose of 250 mg of carbaryl (approximately 2.8 mg/kg) caused immediate symptoms including epigastric pain and sweating in an adult male who intentionally swallowed the chemical. [21] Recovery, after atropine sulfate administration, was complete within a few hours. Male volunteers receiving daily oral doses of 0.12 mg/kg for 6 weeks reportedly exhibited a slight decrease in the ability of the proximal convoluted tubules of the kidney to reabsorb amino acids as indicated by an increase in the urinary amino acid nitrogen to creatinine ratios. [32] The increase in urinary amino acid nitrogen to creatinine ratio is at best a rough measure of the reabsorptive capacity of the proximal renal tubule.

Increased amino acid nitrogen to creatinine ratios seen in humans administered 0.12 mg/kg carbaryl orally, once daily for 6 weeks, were reversible and no increase in the ratios was seen in subjects administered carbaryl at 0.06 mg/kg for the same period of time. [32] These results are difficult to interpret because they were derived from only five subjects given the higher dose. Moreover, determination of ratios was absent and any graphically illustrated data were unimpressive.

Dietary administration of carbaryl to rats for 2 years at 400 ppm and to dogs for 1 year at 7.2 mg/kg resulted in a transient cloudy swelling of the proximal renal tubules in both species. [27] The incidence of renal changes seen in the rats was not significant, and similar changes were noted in treated as well as in control dogs. Marked vacuolization of the proximal tubular epithelium of the kidney in a monkey administered 600 mg/kg of carbaryl for an unspecified period of time was reported. [44,51] It is difficult to draw any conclusion from these studies, [44,51] since only a single electron photomicrograph was presented and the length and

frequency of treatment was not specified. Without other confirming renal tubular function tests in significant numbers of occupationally exposed subjects or animals exposed at various concentrations of airborne carbaryl, the results of the studies previously discussed [27,32,44,51] do not confirm carbaryl-related renal dysfunction in humans. However, sufficient suspicion of carbaryl-related renal effects is established by these studies to warrant a recommendation for surveillance of kidney function in workers. The possibility of effects of carbaryl on the kidney needs further investigation.

No data were found which concerns the effect of carbaryl on any phase of human reproduction. It was reported that carbaryl was not teratogenic in the monkey, [67,69] mouse, [75] rat, [70] rabbit, [71] hamster, [71] or guinea pig, [72] but was teratogenic in the beagle dog [66] and in the guinea pig. [71] Two studies on rhesus monkeys, performed in the same laboratory, were available. The first study [67] made use of 21 mated females, 7 of which were controls. The monkeys were administered carbaryl at oral doses of 2.0 mg/kg (4 animals) and 20.0 mg/kg (10 animals) throughout gestation. No fetal abnormalities were found; however, the abortion rate was high but not dose related. There was a 50% abortion rate (three of six pregnant animals) at the high dose, 100% (two of two pregnant animals) at the low dose, and 20% (one of five) in the controls. The small number of animals used in this study precludes any reliable evaluation of these results. The second study [69] involved 79 monkeys, 48 test and 31 controls. The doses of carbaryl were 0.2, 2.0, and 20.0 mg/kg administered orally from days 20 to 38 of gestation. Abortions occurred in 2 of 16 at the lowest dose, in 1 of 16 at the mid-dose, in 3 of 15 at the highest

dose, in 2 of 15 in vehicle-treated controls, and in 2 of 15 in the untreated controls. It was concluded that carbaryl was not associated with the producing of terata, abortion, stillbirths, or of any other adverse reproductive effects.

Beagle dogs, [66] unlike monkeys, did show reproductive and teratologic abnormalities when administered carbaryl. Oral doses were 3.125, 6.25, 12.5, 25, and 50 mg/kg throughout gestation. Dystocia occurred in 1/3 of treated animals, while decreased numbers of live births occurred at all dose levels, as compared to control dams. There were abnormalities in pups at all dose levels except at 3.125 mg/kg. The litters were smaller than those of the controls in the 25 mg/kg and 50 mg/kg dose groups.

The teratogenic potential of carbaryl was investigated in several other species. Weil et al [70] administered carbaryl in the diet to rats at doses of 20, 100, and 500 mg/kg at various intervals throughout pregnancy or until weaning of the pups. No teratogenic effects attributable to carbaryl were observed at any dose. Carbaryl was administered in gelatin capsules to guinea pigs and rabbits. [71] A dose of 300 mg/kg given either once or daily during days 11-20 of gestation produced a higher incidence of terata in treated guinea pigs than in controls. This dose also induced a high mortality rate in the dams. There was no evidence from rabbits receiving carbaryl at 50, 100, or 200 mg/kg during days 5-15 of gestation of terata when compared to results from pregnant controls. Robens [71] also administered carbaryl by gastric intubation to hamsters at doses of 125 and 250 mg/kg during days 6-8 of gestation. No teratogenic effects were observed at either dose; however,

30% fetal mortality was observed at the high dose, 10% at the low dose, and 5.5% in the control group. Dietary or gastric administration to guinea pigs of carbaryl doses ranging from 50 to 300 mg/kg on days 10-24 of gestation produced no significant increase in the incidence of terata as compared to controls. [72] Mice receiving carbaryl in the diet at 10 or 30 mg/kg from day 6 of gestation to delivery showed no evidence of carbaryl-related terata. [75]

It may be concluded from the above studies [66,67,69-72,75] that carbaryl in doses as low as 6.25 mg/kg is teratogenic in only one species, ie, the beagle dog. [66] The positive findings in the beagle dog and in the guinea pig are not persuasive. In the one study using guinea pigs, [71] terata were produced only at doses which resulted in mortality and morbidity in some of the dams. In another study in the same species, [72] carbaryl administered by gastric intubation or dietary inclusion was found not to be teratogenic. Although carbaryl was found to be teratogenic in the beagle dog at relatively low doses, [66] the dog metabolizes carbaryl differently than the rat, guinea pig, monkey, and, more importantly, humans. [33,34,87] The dog, unlike humans, neither excretes 1-naphthol nor hydroxylates carbaryl. In view of the apparent differences between dog and humans with respect to the metabolism of carbaryl, and the fact that carbaryl was reported not to be teratogenic in the rat [70] and guinea pig, [72] animals that metabolize carbaryl similarly to humans, a standard based on teratogenic effects is not recommended. This recommendation will be reconsidered if results from future research warrant a change.

Reproductive effects of carbaryl in rats have been reported by Shtenberg and Ozhovan [73] in a five-generation reproduction study. Doses

as low as 2 and 5 mg/kg, administered by gastric intubation, produced adverse effects including a decrease in spermatogenesis, a decrease in sperm motility, an increase in the duration of the estrus, a decrease in fertility of females, and a decrease in the survival of pups during the first month of life. In addition, degenerative changes of ovarian and testicular tissue were observed in the rats receiving carbaryl.

Shtenberg and Rybakova [77] administered carbaryl orally to rats of both sexes at doses of 7, 14, and 70 mg/kg for up to 12 months. Growth of the rats was inhibited at 14 and 70 mg/kg, while sperm motility in males also decreased in a dose-related manner after 12 months of treatment. Degenerative changes in the testes, including edema of interstitial tissue and destruction of germinal epithelium, were noted in carbaryl-treated male rats. In females, the estrus cycle was prolonged at the 14 and 70 mg/kg doses. In a three-generation reproduction study on gerbils given carbaryl in the diet (2,000, 4,000, 6,000, and 10,000 ppm), Collins et al [78] reported that no litters were produced at 10,000 ppm in the F3b generation, and that there was a decrease in fertility, pup viability, litter size, and survival of pups (to day 4 and to weaning) which appeared sporadically at all dose levels.

In a similar three-generation reproduction study, Collins et al [78] reported that doses of 5,000 and 10,000 ppm carbaryl in the diet reduced survival of offspring, viability of the pups, and litter size in rats from the first generation on. At 2,000 ppm, only body weight gain of the parents and weanling weight were affected. In contrast, Weil et al [72] did not see any effect when carbaryl was administered by dietary inclusion to rats in a dose range of 7-100 mg/kg. An increased duration of the

gestation period was the only effect seen at 200 mg/kg in the diet. Administration of carbaryl by gastric intubation to rats in a dose range of 3-100 mg/kg showed effects only at the highest dose which included decreased pup viability and litter size, as well as decreased fertility and lengthened gestation period in the females.

The above studies [72,73,77,78] indicate that carbaryl has an effect on several aspects of reproduction in rodents administered carbaryl. Because of the uncertainty in extrapolating reproductive effects seen in animals administered carbaryl orally to those that may be encountered from pulmonary and dermal absorption during occupational exposure, a standard based on these effects is not now recommended. The effects of airborne carbaryl on reproduction is clearly an area for future research.

Mutagenic studies have been carried out in mammalian (mouse) [59] and bacterial systems (E coli, H influenzae, and B subtilis) [63,65] and on yeast (S cervisiae). [64] These studies indicate that, under the experimental conditions used, carbaryl did not demonstrate any mutagenic effects. Experiments on an insect (Drosophila) [62] showed only weak mutagenicity. These studies do not warrant a conclusion that carbaryl is a mutagen. Microbiologic studies on bacterial systems [63,65] and yeast cells [64] indicated that nitrosocarbaryl is a strong mutagen. However, there are no available data indicating that carbaryl is converted by the human body to nitrosocarbaryl. In addition, the reaction would most likely occur at low pH, ie, in the stomach, so it would be applicable to ingested, but perhaps not to inhaled, carbaryl. Thus, from present evidence, it does not seem likely that carbaryl will cause mutations in exposed workers.

The carcinogenic potential of carbaryl has been investigated in mice. [27] Male mice received 10 mg carbaryl subcutaneously once weekly during their 3rd to 8th months of life. There was no increased incidence of tumors over that observed in controls. Innes et al [79] administered carbaryl to mice (4.64 mg/kg) by stomach tube on days 7-28 of age and then in the diet, at a level stated to be equivalent to the amount ingested, for the duration of the experiment, which lasted approximately 18 months. Carbaryl gave no significant evidence of tumorigenicity in this experiment.

Rats were administered carbaryl (50-400 ppm) in the diet for a period of 2 years [27]; there was no dose-related increase in the incidence of tumors over that in controls. In a USSR study, [80] rats received carbaryl at 30 mg/kg twice weekly by the oral route for up to 22 months. A second group of rats were treated with carbaryl (20 mg) by subcutaneous implantation in a paraffin capsule for the same duration. Only 12 of 60 animals receiving carbaryl by the oral route survived, and 4 had cancerous tumors. Only 10 of 48 rats survived treatment with carbaryl subcutaneously and 2 had subdermal fibrosarcomas, neither being at the implantation site. Only one tumor was observed in the control group, in 46 of 48 rats which survived. The high and unexplained death rates in test animals, though the authors suggested little carbaryl toxicity, and the unusual incidence of fibrosarcomas in test and control rats in the absence of a local cause such as implantation, makes this study difficult or impossible to interpret. In addition, there is reason to suspect that the sample used was contaminated by the 2-naphthyl derivative.

Shimkin et al [81] administered N-methyl naphthyl carbamate of their own formulation ip to mice, 0.5 mg 3 times/week for a total dose of 6

mg/mouse over a 12-week period and observed the animals for the development of pulmonary tumors. When compared to other carbamates which were actively tumorigenic in this study, the synthesized compound was classed as giving a marginal response. No information was given as to the purity of the compound synthesized and, more importantly, it is not clear from the structural formula shown in the publication [81] whether 2-naphthyl-N-methylcarbamate or 1-naphthyl-N-methylcarbamate (carbaryl) was synthesized. Consequently, the tumorigenic results reported in the study are impossible to interpret as being carbaryl related. The studies described previously [27,79-81] do not warrant a conclusion that carbaryl is a carcinogen. Future research may clarify the apparent discrepancies in the USSR study [80] and thereby support or refute the implications of the study by Innes et al. [79]

The neuromuscular degenerative potential of carbaryl was investigated in pigs by Smalley et al. [52] Microscopic examination showed skeletal myodegeneration and vasogenic edema of the CNS but not demyelination after 1-3 months of large oral doses (150-300 mg/kg daily) of carbaryl. The toxic effects noted at these doses included tremors, ataxia, incoordination, prostration, and eventual death. [52] Reports of neuromuscular changes such as these have not been found for other species of experimental animals. Carpenter et al [27] administered carbaryl to chickens at very high single subcutaneous doses, 0.25-3 g/kg, and found that leg weakness occurred in 1-2 days at doses higher than 1 g/kg. There was no microscopic evidence of demyelination in tissue sections of the sciatic nerve, spinal cord, and brain. The authors concluded that leg weakness was the only evidence of a transient cholinergic effect in the

chicken. The results of another study in chickens by Gaines [43] lends support to the conclusions of Carpenter et al [27] that carbaryl does not cause demyelination. Male dogs treated with 30 mg/kg of carbaryl iv were found to have less marked signs of intoxication including leg weakness than male pigs treated iv with 20 mg/kg carbaryl. [55] Dietary administration of 125 mg/kg of carbaryl failed to produce overt signs of toxicity in dogs, but did produce spastic paresis of the posterior extremities in pigs. [55] The results obtained with chickens [43,116] and dogs [55] show that apparently only very high doses of carbaryl will produce neuromuscular effects, eg, leg weakness, in these species, probably as a consequence of cholinesterase inhibition. Since no demyelination occurred in the swine [52] nor in the chicken, [27] which is the animal of choice for demonstrating demyelinating effects, it may be concluded that carbaryl is unlikely to produce demyelinating paralytic effects in humans.

The potential for dermal penetration by carbaryl in humans has been established experimentally by Feldmann and Maibach [30,31] and suggested indirectly by Union Carbide Corporation. [13 (sec 9,10)] In addition, absorption of carbaryl occurs through the skin of animals as indicated by death in rats [49] and inhibition of cholinesterase activity in rabbits [39] after dermal application of carbaryl at high doses to these species. However, the quantitative dermal absorption of carbaryl by humans during occupational exposure has not been accurately determined. Adverse local ocular effects have not been reported in humans, but minor eye irritation has been demonstrated in animals after local application of carbaryl. [39] It is therefore concluded that dermal and eye exposure are factors to be considered in the workplace environment. Appropriate work practices to

prevent or limit such contact are thus recommended.

Overexposure to carbaryl in the workplace environment apparently results in a rapid onset of symptoms which leads to voluntary cessation of work and termination of exposure. [13 (sec 13),20] Moreover, employees who have been overexposed to carbaryl in the workplace apparently recover rapidly. [13 (sec 7,13)] Because of a possible additive effect on the inhibition of the enzyme cholinesterase, workers occupationally exposed to both carbaryl and other anticholinesterase agents probably are at a greater risk than those exposed only to carbaryl. Those workers who have a congenital deficiency in cholinesterase enzymes or who routinely take anticholinesterase drugs should be cautioned that they are at a greater risk of intoxication by carbaryl.

The current ACGIH [149] recommended standard of 5.0 mg/cu m was based on the study by Best and Murray, [28] which suggested that over a period of 19 months, workers could tolerate airborne carbaryl concentrations up to 31 mg/cu m. At no time were there any signs or symptoms indicative of anticholinesterase activity, although absorption of carbaryl was verified by measurement of urinary 1-naphthol levels. To provide a safety factor for protection against systemic effects, a Threshold Limit Value of 5.0 mg/cu m was recommended. While available data to derive a safe limit are insufficient, there is no significant evidence indicating that the limit should be changed. In the absence of these needed data, it is proposed that the present workplace environmental limit of 5.0 mg carbaryl/cu m as a TWA concentration be continued.

Available data do not indicate that exposure of workers at this concentration will result in intoxication, and some data suggest that this

limit offers a good margin of safety. However, pertinent investigations, including epidemiologic studies of workers exposed to carbaryl, are needed to validate this recommended limit or, if appropriate, to provide a basis for a better limit.

Sampling and analysis methods were reviewed in Chapter IV. Airborne particulate carbaryl should be collected on a glass-fiber membrane filter mounted with a backup pad in a two-piece closed-face cassette. This sampling method, chosen because it is the best now available, has been shown to provide the required degree of collection efficiency for airborne particulate carbaryl. A colorimetric method was selected for analysis of carbaryl because it is reliable, sensitive, and simple to carry out. The selected method is not entirely specific for carbaryl analysis and several compounds including 1-naphthol can interfere with the precision of the method if they are present in the air sample to be analyzed.

Work practices are discussed in Chapter VI. In operations involving the handling or use of carbaryl formulations, the potential for skin and eye contamination with subsequent absorption is great, and therefore protective clothing and equipment should be worn whenever required to prevent absorption through the skin or contamination of the eye. To minimize percutaneous absorption, employees exposed to carbaryl should wear freshly laundered work clothes before the work shift. They should also shower or bathe and change clothing after the workday. Storage, handling, and eating of food in carbaryl exposure areas should be prohibited to prevent food contamination, and therefore ingestion of carbaryl by employees.

The neurotransmitter function of acetylcholine in the nervous system and the inactivation of acetylcholine by cholinesterase has been discussed in Chapter III. The inhibition of cholinesterase by carbaryl in the nervous system warrants a requirement for preplacement physical examinations directed towards the cardiorespiratory system, the CNS, and the eyes. In addition, such examinations must be made on a yearly basis or at some other interval determined by the responsible physician for employees subject to occupational exposure to carbaryl. It is recommended that preplacement erythrocyte cholinesterase determinations be performed if one of the methods described as suitable in Chapter IV can be used. Such a preplacement determination can serve as a useful comparison in the event of overexposure. Since the kidney is the primary organ for excretion of carbaryl and its metabolites, it is proposed that medical surveillance include a complete urinalysis including microscopic examination.

No information has been found regarding the passage of carbaryl into human milk. As discussed in Chapter III, carbaryl has been found in the milk of dairy animals after their exposure to the insecticide. It seems reasonable to assume that carbaryl may be excreted in human milk, and therefore nursing mothers must be counseled to minimize exposure to carbaryl wherever possible. Research to confirm or refute this assumption should be performed.

It is recognized that many workers are exposed to small amounts of carbaryl or are working in situations where, regardless of amounts used, there is only negligible contact with the material. Under these conditions, it should not be necessary to comply with many of the provisions of this recommended standard, which has been prepared primarily

to protect workers' health under more hazardous circumstances. Concern for workers' health requires that protective measures be instituted below the enforceable limit to ensure that exposures stay below that limit. For these reasons, an action level of carbaryl has been defined as occupational exposure above half the recommended TWA environmental limit, thereby delineating those work situations which do not require the expenditure of health resources for environmental and medical monitoring and associated recordkeeping. This level has been chosen on the basis of professional judgment rather than on quantitative data that delineate nonhazardous areas from areas in which a hazard may exist. However, because of nonrespiratory hazards such as those resulting from skin or eye contact, it is recommended that appropriate work practices and protective measures be required regardless of the TWA concentrations. Similarly, food storage, handling, and eating should be prohibited in carbaryl work areas regardless of TWA concentrations.

VI. WORK PRACTICES

Occupational exposures to carbaryl may occur among people engaged in the manufacture, formulation, or application of the insecticide. Potentially exposed applicators include agricultural workers, spray pilots, and exterminators. [22] Even though absorption of pesticides by the oral and respiratory routes may be more rapid and more complete than by the percutaneous route, the amount of absorption by ingestion and inhalation is probably too small a fraction of the total potential exposure to be considered the main factor in most cases of intoxication of workers in the field. [152] Studies also showed that considerably more insecticide was deposited on exposed skin surfaces than that reaching the respiratory tract. [89,90] The average potential respiratory exposure tended to be higher in agricultural dusting operations than in agricultural spraying operations, while the potential dermal exposure was about the same in both spray and dust applications. [153] Absorption of carbaryl into the body has occurred by three routes of entry: dermal, [30,31] respiratory, [13 (sec 7,9,10)] and oral. [32-34,40] Simpson [90] summarized the relative importance of the dermal and respiratory routes of absorption of carbaryl by orchard spray applicators by stating that, although inhalation exposure is considerably less than dermal exposure, it has an additive effect. Inhalation would be an important factor only if the worker already had experienced sufficient percutaneous absorption approaching a level of absorption at which symptoms occur. [90] Employees occupationally exposed simultaneously to carbaryl and other anticholinesterase agents are at a greater risk because of a possible additive effect on the inhibition of the

enzyme cholinesterase. However, available evidence indicates that the effect would not be potentiated. [48,116] Those employees who have a congenital deficiency in cholinesterase enzymes or who routinely take anticholinesterase drugs should likewise be cautioned against additive effects.

Because the potential for skin contamination, with subsequent absorption of carbaryl through the skin, is great during many handling operations involving carbaryl formulations, [88] use of appropriate personal protective equipment is necessary during such operations to minimize skin exposure. The specific protective equipment required depends on the degree of potential exposure and the body areas that may be exposed. Workers should use all personal protective equipment and exercise all precautions specified on the label of the carbaryl formulation being used.

Protective clothing should be worn wherever required to prevent skin contact with carbaryl. In agricultural situations, personal protective clothing and respiratiors may be the only practical ways to minimize worker exposure. The areas of highest potential exposure for formulating-plant workers have been found to be the hands, forearms, and front of the body; [88] for spray operators, the areas of highest potential exposure have been reported to be the shoulders and back of the neck, [88] the head, arm, chest, shoulders, and back. [90] Hats and other special clothing covering these areas should be used. Long-sleeved coveralls and gloves are recommended for all exposure situations. Fresh clothing should be worn daily. In addition, workers should be advised to shower or bathe after the workday.

In agricultural situations, because of possible bodily contamination by contact with sprayed foliage, as established for other insecticides, [154] immediate entry into sprayed areas should be avoided if possible. Johnson and Stansbury [155] established the half-life of carbaryl on various growing crops to be 2-4 days, and the half-life in soil to be approximately 8 days.

All personnel exposed to carbaryl should wear freshly laundered coveralls or work uniforms (long pants and long-sleeved shirts). [156] Work clothes should be laundered separately from household laundry. If the coveralls or uniform might become wet by mist or spray, use of a waterproof raincoat will provide the best protection for the upper back, shoulders, and forearms, [152] but this may cause discomfort or even heat stress in a hot environment. [157] Under such conditions, wearing long-sleeved clothing such as water-repellant or waterproof clothing that will not be easily penetrated by the insecticide should provide a significant measure of protection. [152]

Protection of the lower trunk and legs from contamination is important where the potential exists for liquid spillage, soaking by continued contact with sprays or sprayed foliage, or penetration of clothing through excessive contact with carbaryl. Waterproof trousers will provide the best protection for the lower trunk and leg areas. [152] Even though the coveralls or uniform is covered by waterproof protective clothing, daily bathing after work [152] and daily changes to freshly laundered clothing [152,157,158] are important for minimizing percutaneous absorption.

The head and neck should be protected from contact with carbaryl. [156] Therefore, some type of protective headgear, such as waterproof rainhats and washable safety hardhats and caps, should be worn. Waterproof or water-repellant parkas also may be used to protect the head and neck at the same time. [156] Personnel potentially exposed to downward drifts of carbaryl [152] should wear wide-brimmed, water-repellant, or waterproof hats to obtain additional protection for the head and neck areas. [152]

Workers handling concentrated wettable powders, concentrated liquids, or finely divided dust formulations should wear protective gloves of natural rubber [156,158] or of neoprene, [159] although the permeability of natural rubber or neoprene to carbaryl remains to be determined. Contact of wet skin with carbaryl should be avoided to minimize absorption.

If an employee might come in contact with concentrated formulations, his hands often will be the body area receiving the highest exposure. Unlined rubber gauntlet gloves, which cover the wrist area not normally protected by the sleeve, provide the best protection. [152] These gloves can be turned wrong side out for proper cleansing of the inside surface.

Use of waterproof footwear is necessary to minimize exposure when the carbaryl formulation may wet the feet. [152] Footwear should be washed and dried thoroughly, inside and out, as frequently as necessary to remove carbaryl contamination. [156]

Safety goggles should be used to minimize eye exposure when spray or dust drift may be encountered, [156] but a face shield is superior to goggles when liquid pesticide is handled. [157] Use of eye protection by pilots applying carbaryl by aircraft is particularly important. Although reports of miosis following eye exposure to carbaryl were not found, Upholt

et al [160] showed that eye exposure of pilots to the cholinesterase inhibitor tetraethylpyrophosphate (TEPP) induced miosis. Infrequent unilateral eye contamination of pilots applying TEPP was found to result in incoordination and reduced ability to judge distance. [160] Although TEPP is a highly toxic organophosphate insecticide and carbaryl is a considerably less toxic carbamate insecticide, carbaryl is also a cholinesterase inhibitor. Therefore, the possibility of the development of these effects after unilateral eye contamination should be considered. The accompanying incoordination could present a significant safety hazard to pilots. [160] It is therefore recommended that pilots engaged in aerial spraying of carbaryl wear goggles.

Respiratory protection as specified in Chapter I must be used whenever airborne concentrations of carbaryl cannot be controlled by either engineering or administrative controls to the workplace environmental limit recommended in this standard. High levels of airborne carbaryl in industry may be present in uncontrolled atmospheres. [13 (sec 10),28]

To minimize absorption of carbaryl through ingestion, employees must not store and use food, beverages, tobacco, or other materials that may be placed in the mouth in the exposure areas. Washing of hands before eating and smoking to further minimize the potential for ingestion is a good practice and should be required.

The employer is responsible for proper disposal of surplus pesticides and pesticide containers. [161,162] Disposal activities should be directed toward minimizing the potential for exposure of personnel to carbaryl and toward minimizing adverse environmental effects. Spills of carbaryl, generally in dry, solid forms, should be vacuumed or shoveled into suitable

containers for subsequent reuse or for transfer to a waste disposal facility. [13 (sec 16)] Liquid spills should be covered with large amounts of absorbent clay and shoveled into disposable containers and the process repeated until the contaminated area is dry. The area is then scoured with hydrated lime and water and the slurry is then blotted with absorbent. [159] The Environmental Protection Agency has established regulations defining prohibited procedures pertinent to the disposal of surplus pesticides and containers (40 CFR 165, published in the Federal Register 39:36867-70, October 15, 1974). Specifically, open dumping is prohibited, and water dumping is generally prohibited. Open burning is also prohibited, except for small quantities of combustible containers, not to exceed 50 pounds or the quantity emptied in a single workday, whichever is less. Such open burning may be performed only where it is consistent with federal, state, or local ordinances. "Open burning" means the combustion of a pesticide, pesticide container, or pesticide-related waste in any fashion other than by incineration in a pesticide incinerator (40 CFR 165, published in the Federal Register 39:36867-70, October 15, 1974). Applicable local, state, and federal regulations should be consulted; if such regulations do not exist, suggested precautions include incineration and burial. Incineration or burial should be performed in a manner not contributing to air or water pollution.

VII. RESEARCH NEEDS

Further research is required to assess the effects of long-term occupational exposure to carbaryl, primarily as airborne dust. There is a need for epidemiologic studies of populations exposed to carbaryl, alone and in combination with other materials, in industry and in agriculture.

Animal studies which focus directly on exposures simulating those of industrial and agricultural workers, including qualitative studies of the effects of exposure to known airborne concentrations, are also important to clarify mechanisms.

The toxicity of carbaryl by various routes of exposure should be correlated with possible variations in absorption, metabolism, and products excreted. Investigation into the validity of urinary 1-naphthol as an indicator of carbaryl exposure is particularly important, since cholinesterase inhibition by carbaryl is readily reversible, and hence of less value in detecting exposure than would otherwise be the case. The suggestion that carbaryl can cause tubular or other renal dysfunction suggested by the amino acid nitrogen to creatinine ratio reported by Wills et al [32] should be studied further to determine whether carbaryl is directly responsible for this effect and the mechanism involved. Since carbaryl is metabolized to 1-naphthol in humans and is excreted in the urine, more information is needed on the toxicity of 1-naphthol and its effect on renal function.

The excretion of carbaryl and its metabolites in milk and its effects on the nursing young should be evaluated in various species. Information

is needed to clarify if carbaryl is excreted in human milk and its effect on the infant.

Further research is needed to support or refute conclusions arrived at in this document about the lack of applicability of available data obtained from experimental animals, on fetal deformities from carbaryl. The mechanism of development of such effects in animals in which fetal abnormalities have been observed, eg, whether they are a sequel of an anti-cholinesterase action or whether they result from toxic action of carbaryl metabolites in such species, should be elucidated. But of even more importance is the development of a national surveillance system that can relate incidences and nature of spontaneous abortions, fetal abnormalities, or developmental defects in children to the occupations and therefore to the exposures of the parents to chemical and physical agents. This would have applicability not only to carbaryl but also to many other occupational hazards.

Research is also needed for clarifying present conflicts in data on mutagenic or carcinogenic effects of carbaryl on mammals. Since nitrosocarbaryl has been shown to be mutagenic in yeast [64] and bacteria, [63,65] the possibility that this compound may be formed in the mammalian body if carbaryl is present should be investigated.

Improved sampling and analytical methods for carbaryl are needed. Materials impervious to all carbaryl formulations should be identified for use in protective clothing.