

**PUBLIC HEALTH GOALS FOR
CHEMICALS IN DRINKING WATER**

CARBOFURAN

August 2000

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**Public Health Goal for
CARBOFURAN
In Drinking Water**

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PREFACE

Drinking Water Public Health Goals
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This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or

MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR CARBOFURAN IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.0017 mg/L (1.7 ppb) is developed for carbofuran in drinking water. Carbofuran is a carbamate pesticide used primarily to control insects on corn and alfalfa. The mechanism of action for carbofuran's activity against insects is its rapid, but reversible inhibition of acetylcholinesterase. Similarly, in animals and humans carbofuran toxicity is characterized by rapid inhibition of neural acetylcholinesterase leading to cholinergic signs. Cholinesterase inhibition is a sensitive indicator relative to clinical effects of exposure to carbofuran in both animals and humans. However, observable signs of toxicity do not always accompany cholinesterase inhibition. An equally sensitive effect observed with carbofuran exposure was testicular changes, notably the amount and nature of sperm produced. Because of the potential for detrimental effects on reproductive function, this endpoint was used in the derivation of the PHG. In the study of Pant *et al.* (1995), male rats were administered carbofuran by gavage at doses of 0.1, 0.2, 0.4 or 0.8 mg/kg, five days per week for 60 days. Decreases in weight were observed for epididymides, seminal vesicles, ventral prostate and coagulating glands at dose levels of 0.2 mg/kg and higher. Decreases in sperm motility, reduced epididymal sperm count and increases in morphological abnormalities of sperm (both number and type) were also noted at dose levels of 0.2 mg/kg and higher. Based on these results, a no-observed-adverse-effect-level (NOAEL) of 0.1 mg/kg-day was identified and used in the development of the PHG. A health-protective concentration of 0.0017 mg/L for carbofuran in drinking water was calculated for a 70 kg adult ingesting two liters of water per day by adjusting the NOAEL for a seven day per week dosing schedule and applying an uncertainty factor of 300 for intraspecies and interspecies variations and the use of a subchronic exposure study. Based on this calculation, the Office of Environmental Health Hazard Assessment (OEHHA) established a PHG of 0.0017 mg/L (1.7 ppb) for carbofuran in drinking water.

The current California maximum contaminant level (MCL) is 0.018 mg/L (18 ppb) and the federal MCL is 0.040 mg/L (40 ppb). Both the California and U.S. Environmental Protection Agency (U.S. EPA) MCLs are based on effects seen in a chronic dog study (ToxiGenics, 1982). California's existing MCL differs from U.S. EPA's MCL in that it recognizes the depression of plasma cholinesterase at a lower dose as a legitimate effect of concern. The current PHG recognizes a more sensitive endpoint from a study not available when the California and U.S. EPA MCLs were developed.

INTRODUCTION

The purpose of this document is to develop a PHG for carbofuran (and its breakdown products) in drinking water. We focus on evaluating the available data on the toxicity of carbofuran. To determine a public health-protective level of carbofuran in drinking water, sensitive groups were identified and considered, and relevant studies were identified, reviewed and evaluated.

Carbofuran is a carbamate pesticide used to control a broad spectrum of insects on corn, rice, alfalfa, grapes, and other foodstuffs. It is sprayed directly onto soil and plants just after emergence to control beetles, nematodes, and rootworm (U.S. EPA, 1995). At present,

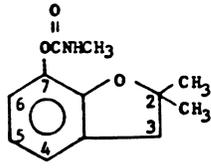
carbofuran is used in agricultural applications throughout California. Carbofuran's pesticidal activity stems from its cholinesterase inhibitory properties. Carbofuran also inhibits cholinesterase in humans and higher animals and has been associated with reproductive toxicity in animals. Federal and state drinking water regulations have been developed for carbofuran. An MCL of 0.018 mg/L was established by the California Department of Health Services (DHS) (22 CCR 64444). This determination was based on a proposed MCL (PMCL) support document recommending the same value (DHS, 1988). The federal maximum contaminant level goal (MCLG) and MCL is 0.040 mg/L for carbofuran (U.S. EPA, 1995). U.S. EPA states that there is no evidence that carbofuran has the potential to cause cancer from lifetime exposures in drinking water (U.S. EPA, 1995). There is no evaluation of carcinogenicity of carbofuran in the Integrated Risk Information Service (IRIS, 1998).

CHEMICAL PROFILE

Chemical Identity

Information related to the identity of carbofuran is provided in Table 1.

Table 1. Identity and Chemical/Physical Properties of Carbofuran (HSDB, 1998; U.S. EPA, 1995)

Property	Information
Chemical Name	2,3-Dihydro-2,2-dimethyl-7-benzofuran-yl-N-methylcarbamate
Chemical Structure	 <p style="text-align: center;">Carbofuran</p>
Chemical Formula	C ₁₂ H ₁₅ NO ₃
Molecular Weight	221.3
CAS number	1563-66-2
EPA Shaughnessy code	090601
Common Name	Carbofuran
Trade Names	Furadan 4F or 3G, Curaterr, Bay 70143, Brifur, crisfuran, D 1221, ENT 271 64, FMC 10242, NIA 10242, Pilarfuran, Kenofuran, Yaltox
Color/Form/Odor	White crystalline solid with slight phenolic odor
Melting point	153-154°C
Vapor Pressure	3.4 x 10 ⁻⁶ mm Hg at 25°C
Octanol /Water partition (K _{ow})Log K _{ow}	2.32
Density/Specific Gravity	1.18 at 20°C
Solubility	0.7 g/L of water at 25°C
Odor/Taste Thresholds	NA
Bioconcentration Factor	117 in one species of fish; not expected to bioconcentrate in aquatic organisms.

Physical and Chemical Properties

Carbofuran is a crystalline solid with limited solubility in water. Important physical and chemical properties of carbofuran are provided in Table 1.

Production and Uses

Since being introduced in 1968, carbofuran has been used to eradicate a broad spectrum of insects on grain crops such as corn and rice, and also alfalfa (U.S. EPA, 1990). However, starting September 1994, carbofuran use has expanded to such United States crops as bananas, pumpkins, cucumbers, watermelons, cantaloupes, squash, dry harvested cranberries, and spinach grown for seed. Carbofuran is registered to be used on sugar cane, rice, corn, alfalfa, cotton, and grapes in California (DPR, 1995). The reported quantity of carbofuran used in California in 1995 was 248,061 pounds (DPR, 1995).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Carbofuran is applied as a flowable or granular product to plants or soils. Based on its measured vapor pressure of 3.4×10^{-6} mm Hg at 25 °C, carbofuran should exist to a limited extent in vapor and particulate phases in the ambient atmosphere. Releases to the atmosphere would occur in relation to the application of carbofuran to plants. Little release is expected from soils containing carbofuran. Removal from the atmosphere could either be by photolysis yielding degradation products, or by sorption onto particles and deposition (HSDB, 1998).

Soil

Once in soil, carbofuran has a varied persistence rate with observed half-lives of several days to over three months. The environmental fate of carbofuran would depend on the organic content, moisture content, and pH of the soil. With high organic content, microbial degradation of carbofuran in soil is rapid. Carbofuran is also decomposed by exposure to sunlight, to yield 2-hydroxyfuradan and furadan phenol (HSDB, 1998).

Water

Carbofuran has limited water solubility, but does migrate with water and has been found in ground water and runoff. In water, carbofuran decomposes with and without microbial degradation. Direct photolysis and photooxidation (via hydroxyl radicals) is thought to be the major pathway to degradation of carbofuran in water. The hydrolysis half-lives in water were found to be 5.1 weeks at pH 7.0 and 1.2 hours at pH 10 (HSDB, 1998). When compared with other insecticides, carbofuran is less persistent than organochlorine and most organophosphorus pesticides whose degradation has been studied in natural water (HSDB, 1998).

Nationwide, carbofuran has been detected (concentrations not reported) in lakes and rivers, particularly near runoff areas. In California, carbofuran has been detected in the

Sacramento-San Joaquin Delta at a maximum concentration of 1.33 µg/L (HSDB, 1998). Carbofuran had been detected in California ground water at levels as high as 5 µg/L reported in a 1988 database (HSDB, 1998). However, carbofuran has not been detected in the most recent pesticide ground water surveys for 1995 (DPR, 1998).

Food

Residues of carbofuran and its breakdown product, 3-hydroxyfuran, have been detected on raw and finished agricultural commodities. Tolerances have been established for carbofuran and its metabolites and breakdown products in various agricultural commodities and meat products (HSDB, 1998).

Other Sources

Apart from agricultural uses, there are no other registered uses for carbofuran as a pesticide.

METABOLISM AND PHARMACOKINETICS

Absorption

Although studies of carbofuran absorption have been limited, there is sufficient evidence to conclude that carbofuran is absorbed readily by the digestive tract upon ingestion. Ahdaya *et al.* (1981) and Ahdaya and Guthrie (1982) studied the absorption and distribution of labeled ¹⁴C-carbofuran by gavage to female ICR mice. Approximately 50 percent of the labeled compound was absorbed in the first 15 minutes, and 65 percent by 60 minutes. In a follow-up experiment, the administration was repeated, but after the stomach was ligated at the pylorus. It was found that 19 percent was absorbed within one hour.

Dermal uptake was studied by application of ¹⁴C-labeled carbofuran to the shaved skin of female ICRT mice (Shah *et al.*, 1981). By measuring the loss of labeled carbofuran compound from the application site, it was determined that 33 percent was absorbed by 5 minutes, 76 percent by 60 minutes and 95 percent by 480 minutes. Except for permethrin, carbofuran was the most absorbed pesticide among several well-known pesticides including carbaryl, parathion, malathion, chlorpyrifos, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT), and others tested in the same study (Shah *et al.*, 1981).

Distribution

Ahdaya *et al.* (1981) and Ahdaya and Guthrie (1982) have studied the distribution of labeled carbofuran given by gavage. The radioactive label was distributed to all organs and rapidly eliminated. Shah *et al.* (1981) applied carbofuran dermally, and found the highest concentration in excretory products (72 percent) followed by the carcass (12 percent), stomach (3 percent), intestine (3 percent), liver (1 percent), and blood (0.8 percent). The remaining carbofuran (less

than 1 percent of the total) was found in soft tissues. The carcass is the portion of the body remaining after removal of the listed organs.

Metabolism

Metabolism of carbofuran has been evaluated in rats, mice, insects, and plants. The known pathways for carbofuran metabolism are illustrated in Figure 1. It appears that the main route consists of oxidation at the benzylic carbon to yield 3-hydroxycarbofuran, which can then be hydrolyzed to 3-hydroxycarbofuran phenol and 3-ketofuran-7-phenol. Another pathway of metabolism, which is more common in mammals than insects and plants, is to hydrolyze carbofuran directly to the carbofuran phenol (U.S. EPA, 1990; Metcalf, 1968).

The anticholinesterase properties of the three major carbofuran metabolites were evaluated; particularly those with intact carbamyl moieties. The moieties, 3-hydroxycarbofuran, 3-ketocarbofuran, and 3-hydroxy-N-hydroxy-methylcarbofuran were found to have less anticholinesterase activity than carbofuran itself (Dorough, 1968; 1983).

Excretion

Administered carbofuran is rapidly excreted. Ahdaya *et al.* (1981) reported that after 60 minutes, 6 percent and 24 percent of the dose from labeled carbofuran was detected in the exhaled breath and urine of mice, respectively. Shah *et al.* (1981) found that after eight hours of dermal administration, 72 percent of the dose was eliminated with approximately 2/3 in the feces and 1/3 in the urine of mice. The dose excreted by feces was approximately half of the administered dose.

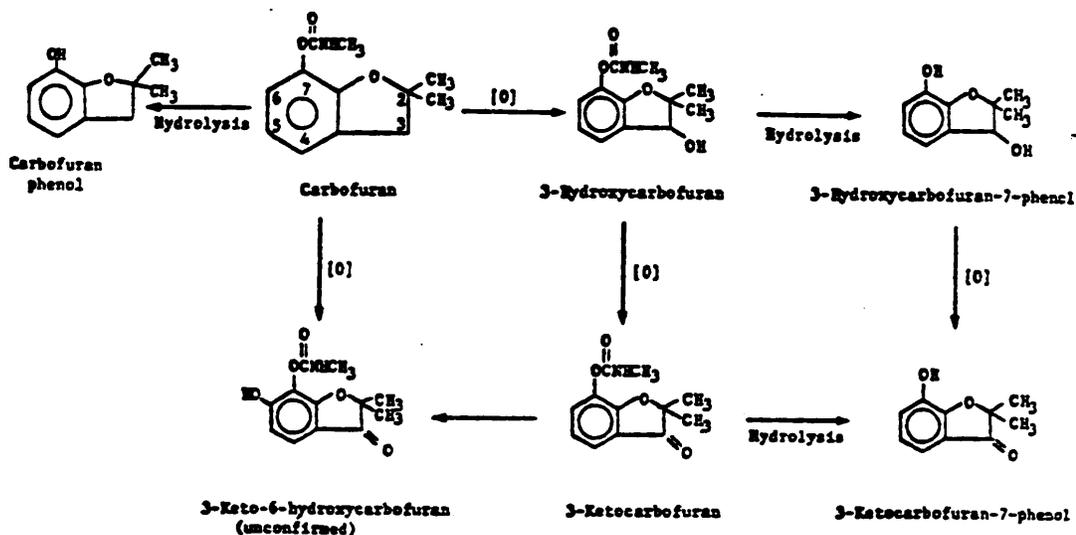


Figure 1. Oxidation and Hydrolysis of Carbofuran (U.S. EPA, 1990).

Carbofuran can be either oxidized or hydrolyzed depending on the conditions in animals, insects and plants. In animals, it is likely to be oxidized to 3-hydroxycarbofuran, then to 3-ketocarbofuran.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

The acute toxicity of carbofuran has been evaluated in several species. The reported oral LD₅₀s are 6.4 to 14.1 mg/kg for rats, 18.5 mg/kg for dogs, and 25 to 38.9 mg/kg for chickens (U.S. EPA, 1990). Mice appear to be less sensitive to the toxicity of carbofuran as the median lethal doses ranged from 250 to 500 mg/kg (Wolfe and Esher, 1980).

The lethal effects of carbofuran are due largely to the chemical's direct inhibition of acetylcholinesterase. Ultimate cause of death is respiratory failure. Signs and symptoms of cholinesterase poisoning occur within minutes as carbofuran acts directly on the enzyme without metabolic activation (Tobin, 1970). Variations in species sensitivity probably reflect species differences in metabolic deactivation of carbofuran to its less potent metabolic products.

Subchronic Toxicity

Several studies have been performed to evaluate the subchronic toxicity of carbofuran.

Five female rats were exposed by means of oral intubation to single doses of 0.2, 0.5, 1.0, 3.0 or 10 mg/kg (FMC, 1971a). Red blood cell (RBC), plasma, and brain cholinesterase measurements were taken at 1, 2, 4 and 24 hours after dosing. Significant depressions in cholinesterase activity were observed at 0.5 mg/kg and above for all types of cholinesterase, but brain cholinesterase was the most depressed. Another study (FMC, 1971a) exposed five female rats to 1.0 mg/kg for 14 days or 28 days. Inhibition of brain cholinesterase of 32 and 27 percent was noted after 14 and 28 days, respectively. Plasma cholinesterase was inhibited at 32 and 27 percent after 14 and 28 days, respectively. RBC cholinesterase was inhibited slightly at levels less than 20 percent. Inhibition of cholinesterase was rapidly reversible, and it was not cumulative over time. The no-observed-adverse-effect-level (NOAEL) for these studies was 0.2 mg/kg due to the depression of brain cholinesterase.

After these dose-ranging studies, FMC (1971b) conducted a 90-day study in rats given carbofuran by gavage at 0, 0.1, 0.3, 1.0 or 3.0 mg/kg-day. RBC and plasma cholinesterase activities were measured at days 15, 30, 45 and 60 minutes after treatment. No brain cholinesterase assessments were made. High dose groups exhibited depressions up to 31.7 and 53 percent for RBC and plasma cholinesterase, respectively. Depressions in cholinesterase activity were reversed within hours of treatment.

In a subchronic study in dogs, carbofuran was administered to three dogs/sex/group in gelatin capsules at doses of 0, 0.025, 0.25, 1.25, 2.5 or 5.0 mg/kg-day for 92 days (FMC, 1971a). Blood cholinesterase measurements were made on days 72 and 113 at 15, 30, 45 and 60 minutes after treatment. Substantial cholinesterase depression was noted in both plasma and RBC measures at the highest dose groups (over 50 percent).

Genetic Toxicity

Carbofuran has been tested in numerous studies for mutagenicity and genotoxicity. These are summarized below.

The results of these studies indicate that carbofuran could possibly be a weak mutagen. Carbofuran was positive for mutagenicity in Ames tests from one lab (Moriya *et al.*, 1983), but not in several other tests using the same Salmonella strains (see Table 2). Marginal to weak positive results were noted in strain 1535 without S-9 activation in tests conducted by Microbiological Associates but not in tests with the same strain from other laboratories (Table 2). Carbofuran was not found to be mutagenic in E. coli reversion, yeast conversion, *Z. mays* (corn) back mutation, unscheduled DNA synthesis in human lung fibroblasts, Drosophila sex-link recessive, chromosome aberration in Chinese hamster ovary cells TK+/-, sister chromatid exchange in Chinese hamster ovary cells and cytogenetic assays in Sprague-Dawley rats. Carbofuran was weakly positive in the mouse lymphoma assays without activation and in Chinese hamster V-79 cells for ouabain resistance.

Table 2. Genetic Toxicity Studies of Carbofuran

ASSAY	DOSE	RESULTS ^a (0, S9)	REFERENCE
Ames			
TA98, 100, 1535, 1537, 1538	Up to 19 mg/plate	-, -	Waters <i>et al.</i> , 1982
TA98, 100, 1535, 1537, 1538	10 µg/plate	-, -	Gentile <i>et al.</i> , 1982
TA98, 100, 1535, 1537, 1538	10 µg/plate	-, -	Gentile <i>et al.</i> , 1982
TA98, 1538	Up to 10 mg/plate	+, +	Moriya <i>et al.</i> , 1983
TA100, 1535, 1537	Up to 5 mg/plate	-	Moriya <i>et al.</i> , 1983
TA98, 100	Up to 25 µg/plate	-, -	Nelson <i>et al.</i> , 1981
TA 1535, 1537, 1538, 100,	Up to 5 mg/plate	-, -	SRI, 1979
TA1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, ¹	MA, 1983a
TA1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, ¹	MA, 1983b
TA1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, ²	MA, 1983c
TA1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, ²	MA, 1983d
TA1535, 98, 100	Up to 10 mg/plate	-, ²	MA, 1983e
TA1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, ²	MA, 1983f
TA1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, ³	MA, 1983g
TA1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, ³	MA, 1983h
TA 1535, 1537, 1538, 98, 100	Up to 10 mg/plate	-, -	LB, 1983

^a + = positive results, - = negative results

¹ Weak positive increase (>2X) in TA 1535 without S9 only.

² Weak positive increase (>2X) in TA 1535 without S9 only.

³ Weak positive increase (>2X) in TA 1535, TA 1537, and TA 100 without S9 only.

Table 2. Genetic Toxicity Studies of Carbofuran (concluded)

ASSAY	DOSE	RESULTS (0, S9)	REFERENCE
Other Microbial			
<i>E. coli</i> Wp reversion	Up to 10 mg/plate	-, -	Waters <i>et al.</i> , 1982
<i>E. coli</i> Wp reversion	Up to 5 mg/plate	-, -	Moriya <i>et al.</i> , 1983
<i>E. coli</i> Wp reversion	Up to 5 mg/plate	-, -	SRI, 1979
Yeast gene conversion	Over 2-3 logs	-, -	Gentile <i>et al.</i> , 1982
Other Assays			
<i>Z. mays</i> , back mutation	2.24 kg/ha	-	Gentile <i>et al.</i> , 1982
UDS human lung fibroblasts	5 doses	-, -	Waters <i>et al.</i> , 1982
Mouse lymphoma	0-211 µg/mL	+	MA, 1983i
Mouse lymphoma	0-316 µg/mL, 0-1780+S9	+, -	MA, 1983j
<i>Drosophila</i> sex-link recessive	0.75 ppm	-	U of Wisc, 1983
<i>Drosophila</i> sex-link recessive	0.10 ppm	-	WARF, 1981
<i>Drosophila</i> sex-link recessive	0, 5, 10 µg/mL	-	LB, 1983
Chromosome aberration CHO	Up to 2.4 mg/mL	-	MA, 1983k
Chromosome aberration CHO	Up to 2.4 mg/mL	-, -	MA, 1983l
Sister chromatid exchange	Up to 2.5 mg/mL	-, -	MA, 1983m
Sister chromatid exchange	Up to 2.5 mg/mL	-, -	MA, 1983n
Cytogenetic assay in rats	0-6.0 mg/kg	-	MA, 1983o
Cytogenetic assay in rats	0-10 mg/kg	-	MA, 1983p
V-79, ouabain resistance	0.01, 0.5, 1.0 mM	+, - ¹	Wojciechowski, <i>et al.</i> 1982

¹ activation by radiation

Developmental and Reproductive Toxicity

The FMC Corporation conducted several teratology studies with carbofuran in the rat and in the rabbit. In a dose-ranging study (IRDC, 1980a), 20 pregnant female Charles River CD rats were fed diets containing 0, 20, 60, 120, 160 or 200 ppm of carbofuran during gestation days six through 19. These dose levels correspond to applied doses of 0, 1.0, 2.9, 5.8, 7.7, and 9.7 mg/kg-day assuming a body weight of 0.290 kg and a food consumption rate of 0.014 kg/day. There was 100 percent survival in all groups. Maternal body weight gain was decreased during the first two days of treatment in the 120, 160, and 200 ppm groups. Neonatal weight decreases were noted at the two highest dose groups. No other toxicity or clinical signs were noted.

In a follow-up study (IRDC, 1981a), 40 pregnant females Charles River CD rats were fed 0, 20, 60, or 160 ppm in the diet (daily doses 0, 1, 2.9 and 7.7 mg/kg-day) during gestation days six through 19. One-half of the fetuses were examined for visceral and skeletal abnormalities on

gestation day 20. Remaining dams delivered normally and the pups were mothered until lactation day 21. There were no clinical signs. Food consumption was normal in the 20 and 60 mg/kg groups but was reduced by 6 percent in the 160 ppm group. Maternal body weight gains were significantly reduced in the 60 and 160 ppm groups. No effects were noted in the length of gestation, parturition, physical appearance of pups, or any pup survival indices. Mean pup weights were slightly reduced at 60 and 160 ppm but attributed to the reduction of maternal body weight. No malformations were observed in any group. A NOAEL of 20 ppm (1.0 mg/kg-day) was identified from this study.

Carbofuran was administered to 10 to 12 CD rats by gavage at 0, 0.05, 0.1, 0.5, 1.0, 3.0 or 5.0 mg/kg-day from days 7 to 19 of gestation (Courtney *et al.*, 1985). Carbofuran was maternally toxic at doses of 1, 3, and 5 mg/kg. Fetal toxicity was significant at 5 mg/kg level and included reduced number of live fetuses per litter or increased fetal mortality or decreased fetal body weight. No significant changes in these parameters at lower doses were noted when compared with controls. In the same study, rats were also administered 0, 0.1, 1, 5, 10 or 20 mg/kg-day carbofuran by gavage. There was high maternal mortality at the two highest doses of 10 and 20 mg/kg. There was also higher fetal mortality and a decrease in implantation rate at the two highest doses. No significant increases in malformations related to dose were noted in either study.

Twenty (seven-month old) female New Zealand rabbits were administered 0, 0.12, 0.5 or 2.0 mg/kg-day carbofuran by oral gavage on days 6 through 18 of gestation (IRDC, 1981b). One of the dams in the high dose group died on the eleventh day of gestation from unknown causes. The other animals experienced a 20 percent reduction in body weight gain during the treatment period. No malformations were observed in any of the treatment groups. No differences in the number of fetuses, litter weight, or developmental or genetic abnormalities were observed in any of the carbofuran-treated animals when compared to the control group. Three dams aborted toward the end of the gestation period, one from each of the treatment groups. Therefore, there was no dose-related response for this finding.

In a three-generation study in rats (FMC, 1979), reproductive effects were evaluated. Weanling Charles River rats were administered 0, 20 or 100 ppm carbofuran in the diet, corresponding to approximately 0, 1, and 5.0 mg/kg-day based on assumed body weight of 350 mg and a daily food consumption of 14 grams. Generations one and two consisted of 10 males and 20 females per group, and generation three contained 10 males and 24 females. Behavior and survival were observed daily, as well as body weight, growth size, male and female fertility, gestation time, litter size and viability and survival of pups through weaning. No effect on either female or male fertility or on the length of gestation was observed at either dose level. Litter size and growth were comparable to controls in both treatment groups in all three generations. The viability and survival of pups were largely unaffected by carbofuran, except that survival of the first litter of the 100 ppm group was slightly lower by day four of lactation. The authors concluded that the NOAEL for carbofuran using reproductive effects as an endpoint was 20 ppm, corresponding to a dose of 1.0 mg/kg bw-day.

Effects on sperm quality and amount of ejaculate from carbofuran exposure were studied by Yousef *et al.* (1995). In this study, 20 mature male New Zealand white rabbits, eight months of age, were divided into four groups each receiving 1/100 or 1/10 of the LD₅₀ (unspecified doses). The authors reported an overall decline in the body weight and a decrease in the amount of sperm released following treatment. The latter effect was most evident with the higher dose.

Carbofuran was administered orally to adult male rats at levels of 0.1, 0.2, 0.4 or 0.8 mg/kg for five days per week for 60 days (Pant *et al.*, 1995). A dose-dependent decrease in body weight of rats was observed in the range of 0.2 to 0.8 mg/kg. Decreases were observed in selected organ

weights including the epididymides, seminal vesicles, and ventral prostate and coagulating glands at dose levels of 0.2 mg/kg and above. Decreases in sperm motility, reduced epididymal sperm count and increases in morphological abnormalities of sperm (in type and number) were also noted at dose levels of 0.2 mg/kg and above. Significant changes in activity were noted for various testicular enzymes including sorbitol dehydrogenase (SDH), glucose 6-P-dehydrogenase, lactate dehydrogenase (LDH) and gamma glutamyl transpeptidase at doses of 0.2 mg/kg and above. The NOAEL identified from this study is 0.1 mg/kg based on toxicity observed at the higher doses.

Pant *et al.* (1997) also investigated the effects of carbofuran on male offspring of treated female rats. Female Drucker rats were mated, and after confirming that pregnancy had occurred the female rats were divided into two groups and given either peanut oil or peanut oil with 0.2 or 0.4 mg/kg carbofuran daily. Treatment was stopped at parturition. After attaining 90 days, pups were sacrificed. The testes, epididymides, seminal vesicles, ventral prostate, and coagulating glands were quickly removed and weighed. No general pathological effects were observed with either treatment. Significant variation in enzymatic activities was noted with SDH, LDH and γ -glutamyl dehydrogenase (γ -GT) in the 0.4 mg/kg dose group only. Decreases in sperm motility and sperm count, along with an increase in abnormal sperm counts were also noted at 0.4 mg/kg-day. Histopathological examination revealed atrophied seminiferous tubules and degenerative changes to Sertoli cells at 0.4 mg/kg-day. The lowest dose of 0.2 mg/kg-day is considered a NOAEL for these effects.

In a three-generation study, mink were fed 0.05 mg/kg-day carbofuran from weaning to the weaning of the next generation (Beard and Rawlings, 1998). No overt signs of toxicity were noted in any treated animals and there were no changes in serum concentrations of testosterone, estradiol and cortisol. No effects on reproductive capacity were noted.

Immunotoxicity

A standard skin sensitization study was performed on guinea pigs (FMC, 1971c). Ten intradermal injections of 0.1 percent carbofuran in propylene glycol were given at 48-hour intervals. A challenge dose was applied two weeks after the tenth injection. No sensitization was evident.

Barnett *et al.* (1980) investigated the effect of carbofuran on development and serum immunoglobulins in mice. Female mice were administered 0, 0.1 or 0.5 mg/kg-day carbofuran in the diet throughout gestation. Pups were then monitored for up to 800 days. No effects were noted on litter size, viability or body weights (some weight fluctuations at the high dose). Serum gamma globulins were largely unaffected. A transient higher level of IgG₁ was seen at the high dose at the 101 and 400 day sacrifices, but not at 800 days. Other fluctuations in levels of gamma globulins were noted, but did not appear to be dose-related.

Neurotoxicity

The hallmark of carbofuran toxicity is inhibition of cholinesterase activity in the nervous system. There are two basic types of cholinesterase measurements. Blood cholinesterase levels are the easiest to measure, as they require only blood samples and do not necessitate the termination of the subject. Blood cholinesterase measures consist of plasma cholinesterase or RBC (true) acetylcholinesterase. These measures serve best as markers of exposure, as they are not directly linked to acetylcholinesterase in central or peripheral nerves. Evaluation of functional acetylcholinesterase requires taking tissue samples, most commonly of brain or muscles.

Depression of nerve or neuromuscular acetylcholinesterase is most indicative of adverse effects, while depression of blood cholinesterase provides a useful indicator of potential impairment. However, acetylcholinesterase assays for carbofuran and other carbamates must be done quickly and carefully because of the reversible nature of the cholinesterase inhibition by carbamates.

Cambon *et al.* (1979) administered by intubation 0, 0.05, 0.25 or 2.5 mg/kg carbofuran to groups of eight pregnant Sprague-Dawley rats on gestation day 18. Rats were killed 1, 5, and 24 hours after dosing and cholinesterase activity was measured in fetal and maternal blood, brain, and liver. Clinical signs of cholinesterase poisoning consisting of tremors, salivation, miosis, dyspnea, and piloerection appeared at the highest dose within five minutes, with high mortality. Maximum acetylcholinesterase inhibition was found only in certain tissues one hour after treatment. Acetylcholinesterase depression in maternal blood was 15 percent at the 0.05 and 0.25 mg/kg doses, and 21 percent at the 2.5 mg/kg dose, with high variability. Depression of cholinesterase in fetal blood was higher than maternal, 32 percent at 0.05 mg/kg, 27 percent at 0.25 mg/kg and 37 percent at 2.5 mg/kg. Maternal brain acetylcholinesterase depression appeared to be dose-related with 15 percent at 0.05 mg/kg (not significant), 31 percent at 0.25 mg/kg, and 56 percent at 2.5 mg/kg. Fetal brain acetylcholinesterase was depressed only at the highest dose. Based on maternal brain acetylcholinesterase depressions recorded in this study, a lowest-observed-adverse-effect-level (LOAEL) of 0.25 mg/kg and a NOAEL of 0.05 mg/kg are identified.

The binding of carbofuran with carboxylesterases (as well as blood cholinesterases) may prevent the direct action of carbofuran on acetylcholinesterase. Gupta and Kadel (1989) showed that pretreatment of rats with nonspecific esterase inhibitor iso-OMPA (1 mg/kg, subcutaneous) one hour prior to carbofuran administration of 0.5 mg/kg potentiated carbofuran toxicity by more than three-fold. The rats showed severe signs of cholinergic depression. When each drug was given alone (iso-OMPA at 1 mg/kg and carbofuran at 0.5 mg/kg) significant depression of carboxylesterase activity was observed in brain structures, while acetylcholinesterase activity was unaffected.

Chronic Toxicity/Carcinogenicity

Long-term studies have been performed to evaluate carbofuran toxicity in several species.

Rotaru *et al.* (1981) fed ten male Wistar rats/group carbofuran in the diet for 180 days at levels of 0, 10 or 25 ppm. When adjusted for final rat body weight, the approximate doses are 0, 0.49 and 1.18 mg/kg-day assuming a daily food consumption of 0.014 kg. The animals were analyzed histologically and serum enzymes were evaluated. No differences in body weight increases or liver weight changes were observed. The only elevated serum enzyme was lactic dehydrogenase and it occurred only at the 10 mg/kg dose. No significant dose-related changes were noted. However, neither serum nor RBC cholinesterase activities were measured. Therefore it cannot be confirmed that rats were exposed to sufficient levels of carbofuran to observe toxicity.

Wolfe and Esher (1980) fed "old-field mice" (*Peromyscus polionotus*) and cotton mice (*P. gossypinus*) 100 ppm of carbofuran for eight months. This concentration corresponds to an estimated dose of 19.6 mg/kg-day for *P. polionotus* and 12.2 mg/kg-day for *P. gossypinus* (based on body weights of 13.8 or 29.5 grams and a reported daily food consumption of 2.7 or 3.6 g for each respective strain). Animals were kept as pairs (male and female) along with their offspring. Food consumption, mortality, reproduction (number of litters, litter size and percent survival), and age at appearance of selected developmental characteristics of young were monitored throughout the duration of the experiment. Male survivors were tested in a behavioral maze at

the end of the treatment period. There was no indication of cumulative or delayed effects from dosing, except for possible delayed mortality in *P. polionotus*.

In another study (IRDC, 1979b), groups of 90 Charles River CD rats were administered carbofuran at 0, 10, 20 or 100 ppm in the diet for two years, corresponding to approximately 0, 0.5, 1.0 and 5 mg/kg-day. Interim sacrifices were made at 6, 12, and 18 months. Parameters observed included body weight, food consumption, behavior, ophthalmoscopy, hematology, blood chemistry, and histopathology. All animals, whether healthy or moribund, or interim sacrifices were examined histologically. Over 40 organs were evaluated histologically, some with multiple sections. The only statistically significant change observed upon treatment was a slightly decreased group mean body weight for males at 5 mg/kg-day throughout the study. No effects on cholinesterase were noted at 0.5 or 1 mg/kg-day, while at 5 mg/kg-day there was statistically and biologically significant plasma, RBC and brain cholinesterase depression. In the brain, there was up to 21 percent inhibition in male and 43 percent inhibition in female cholinesterase activity. The incidence of rats with neoplasms across all histological classifications was comparable for all groups, except for the incidence of total tumors in females at the highest dose group. For these high dose females the higher total tumor incidence could not be attributed to an increased incidence in any one particular tumor type, and therefore confirmed no particular relationship with treatment. Neoplasms and nonneoplastic lesions, whether by type, incidence or degree of severity were judged to be spontaneous or typical of the type of lesions expected for this strain of animals at their age. The NOAEL for this study was determined to be 1.0 mg/kg-day.

In a parallel study, FMC Corporation (IRDC, 1980) evaluated effects of carbofuran on 100/sex/group of Charles River CD-1 mice which were administered 0, 20, 125 or 500 ppm in the diet (0, 2.5, 12.5 and 50 mg/kg-day). A complete profile of parameters was evaluated as in the previously described rat study. At the highest dose (50 mg/kg-day), there was a significant decrease in body weight in male rats up to 78 weeks, and in female rats up to 65 weeks. No other effects were noted except at the two highest doses, where significant reductions in brain cholinesterase occurred in both males and females. No effect on plasma or RBC cholinesterase was observed at any of the dose levels during the experiment. No treatment-related increases in neoplasms or nonneoplastic changes were observed. All observed tumors occurred at rates expected for the strain and reflected similar incidences among control and treatment groups.

A one-year dietary study was performed on beagle dogs (ToxiGenics, 1983). Four groups of beagle dogs (each consisting of six male and six female dogs) were given daily dose of 0, 10, 20 or 500 ppm carbofuran in the diet (approximately 0, 0.27, 0.54 and 13.5 mg/kg-day for males and 0, 0.2, 0.4, and 12.0 mg/kg-day for females). The animals were allowed access to the treated food for two hours each day. Biochemical, hematological, and clinical parameters were monitored, evaluated, and reported. Histopathological examination of all major organs was undertaken. At 500 ppm, there was weight loss in 9 out of 12 dogs with one death. The weight loss was attributed to starvation due to food emesis, and this was confirmed by the presence of loose stools. A dose-dependent depression of plasma cholinesterase in males was highly significant. Plasma cholinesterase inhibition at 3, 7 and 14 days was 18 to 20 percent at 10 ppm, 24 to 27 percent at 20 ppm and over 77 percent at 500 ppm, respectively. At 500 ppm, there was marked depression of plasma cholinesterase in female dogs and a consistent reduction in RBC cholinesterase. A 24 percent decrease (not significant) in brain cholinesterase activity in male and a 44 percent decrease in brain cholinesterase activity in female dogs were observed at 500 ppm. Other toxic signs observed at 500 ppm included a 40 percent reduction in body weight, alopecia in both sexes, abrasions of the ear in males, changes in hematocrit, hemoglobin levels and erythrocyte counts, and mild to moderate inflammatory changes in the lung. Electrolyte levels were significantly altered as well at the high dose and included depressions in calcium and

sodium levels and elevated potassium levels. There was also treatment-related testicular degeneration with some aspermia in four of the five males at 500 ppm. One of the six males at 20 ppm had testicular degeneration. In female dogs at 500 ppm, a few instances of uterine hyperplasia and hydrometria were observed. No tumors were reported. A NOAEL of 20 ppm (0.54 mg/kg) was identified for dogs based on the weight loss, food emesis, early signs of testicular dysfunction and hematological effects. Because of the significant inhibition of plasma cholinesterase (as reported in DHS, 1988) at 20 ppm (0.54 mg/kg), this lowest dose could also be considered a LOAEL. U.S. EPA concluded that 20 ppm (0.50 mg/kg) was a NOAEL based on absence of cholinesterase effects and testicular effects. It stated that statistically significant plasma cholinesterase inhibition at 20 ppm was not biologically significant (U.S. EPA, 1990).

Toxicological Effects in Humans

Acute Toxicity

No cases of human lethality have been reported as a result of carbofuran exposure. However, there were cases of carbofuran intoxication in applicators and formulators primarily following inhalation (Tobin, 1970). Symptoms from inhalation exposure included mild and reversible symptoms of acetylcholinesterase depression such as malaise, sweating, light-headedness, nausea, blurred vision, hypersalivation, and vomiting. These symptoms were observed within two hours of exposure and the affected persons apparently recovered completely within five to six hours without treatment, or within the half hour with atropine.

In a recent California incident, 34 farm workers in Fresno County became ill after early reentry into a cotton field that had been sprayed two hours earlier with a carbofuran-containing pesticide formulation (active ingredients 0.26 percent carbofuran, 0.05 percent abamectin, and 0.05 percent mepiquat chloride [a growth regulator]) (Das *et al.*, 1999). The reentry interval for use of carbofuran on cotton is 48 hours. Symptoms included nausea, headache, eye irritation, muscle weakness, tearing, vomiting, and salivation. Bradycardia, diaphoresis, and miosis were also reported. Most of the workers who reported symptoms were evaluated at a local medical clinic and released the same day; one was hospitalized overnight for atrial fibrillation. Cholinesterase assays were somewhat equivocal, although 10 workers had RBC cholinesterase values lower than laboratory normal. Potential longer-term, residual effects are still being evaluated.

At a much higher dose of a carbofuran pesticide formulation resulting from intentional ingestion, more severe and life-threatening effects have been reported, including coma and respiratory failure (Baban *et al.*, 1998).

FMC (1977) conducted controlled human studies with single doses of carbofuran. Two male subjects were given a single dose of 0.05 mg/kg carbofuran following breakfast. No effects were reported at 0.05 mg/kg. Another two male subjects receiving 0.10 mg/kg reported headache and light-headedness (judged by the researchers as not exposure-related). Four male subjects administered 0.25 mg/kg carbofuran after breakfast exhibited overt signs of cholinesterase depression including dry mouth, salivation, diaphoresis, abdominal pain, drowsiness, dizziness, anxiety, and vomiting. Pupil size was affected only at 0.25 mg/kg carbofuran. Red blood cell cholinesterase was depressed in a dose-dependent fashion; plasma cholinesterase was not. From these data, a NOAEL of 0.05 mg/kg can be identified for clinical signs associated with cholinesterase depression.

FMC (1977) also conducted studies on the effects of dermal application of carbofuran on human subjects. Carbofuran at a concentration of 0.5 mg/kg/cm² or higher was applied to the skin of two

males. At 2 mg/kg, under conditions of high temperature and humidity with mild exercise, depression of RBC cholinesterase was observed with minor symptoms of cholinesterase toxicity. When the dose was increased to 32 mg/kg under conditions of reduced temperature (70°) and half the humidity, no depression of cholinesterase was observed or symptoms. Another dermal study comparing the effects of Furadan 4 F and FMC 35001 was conducted with the application of these compounds for four hours, after which the compound was washed off (Arnold, 1978). Red blood cell cholinesterase was inhibited by 15 percent at 0.5 mg/kg, 25 percent at 1.0 mg/kg, 41 percent at 2.0 mg/kg and 55 percent at 4.0 mg/kg. Plasma cholinesterase inhibition fluctuated with no apparent dose-related trend.

Twenty-five workers at two pesticide-formulating plants were diagnosed as suffering from carbofuran poisoning after presentation with symptoms consistent with cholinesterase inhibition, including myosis, dizziness, weakness, blurred vision, nausea, and sweating (Huang *et al*, 1998). In one of the plants, blood cholinesterase activity was reported to be significantly depressed compared to pre-shift values. Pallor, epigastric pain, vomiting, and muscle fasciculation was also noted in a few cases. In most cases, recovery was complete within two to three hours, with or without atropine treatment, after workers were removed from the pesticide exposure. Carbofuran concentrations in air were measured at 0.025 to 1.12 mg/m³ in the plant where cholinesterase inhibition was documented, and 0.018 to 0.067 mg/m³ in the other. The available exposure information was inadequate to calculate a NOAEL

Chronic Toxicity and Carcinogenicity

No reports of longer-term epidemiological studies on the effects of carbofuran have been found.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The major toxicity of carbofuran is cholinergic crisis precipitated by depression of acetylcholinesterase both centrally and peripherally, potentially leading to death at high enough doses. Apart from the potential testicular toxicity, there is little evidence for cumulative or chronic toxicity of carbofuran to the major organs. This is probably due to the limited duration of carbofuran in the body as it is rapidly metabolized by hydrolysis, chiefly by cholinesterases and carboxylesterases (which it also inhibits) and is not dependent on the liver for its removal. Therefore, for the purposes of developing a PHG for carbofuran in drinking water, where evaluating risks from long-term exposure is important, data from studies of all durations, and not exclusively chronic studies, might be appropriate.

Depression of cholinesterase can be suitable as an endpoint and is considered for use in PHG development. However, direct measures of acetylcholinesterase (AChE) in neural and neuromuscular junctions are not always available. The other endpoints are indirect measures of AChE, i.e., the activities of plasma and RBC cholinesterase. The latter is considered a “true” AChE, identical to the form found in the nervous system. Plasma cholinesterase (or pseudocholinesterase) is a different enzyme from that involved in neural transmission; it has an active site similar to that of AChE and has optimum activity with slightly larger substrates such as butyrylcholine. Plasma cholinesterase has no established function in the body. Carbofuran also inhibits other enzymes, most notably carboxylesterases, which are found throughout the body and are involved in many physiological reactions. The significance of carboxylesterase inhibition is

not known and may or may not be related to testicular effects noted in several studies. Studies evaluating carboxylesterase activity upon carbofuran exposure have been very limited.

Another endpoint for consideration for risk assessment would be effects of carbofuran on the testes. As noted in the short-term studies of Pant *et al.* (1995, 1997) and Yousef *et al.* (1995), effects include some evidence of degeneration of tubules, aspermia, and decreased sperm counts. There is evidence of testicular degeneration at higher doses used in the chronic dog study (ToxiGenics, 1983). No overt toxicity to reproductive organs or impaired reproductive function was evident in subchronic, chronic, three-generation or teratogenicity studies conducted in rodents or mink. Slight decreases were noted in rat pup survival in one study (Courtney *et al.*, 1985), but only at maternally toxic doses. No evidence for decreased fertility was noted.

Candidate studies for PHG derivation (those which have reported effects at very low doses) and their respective NOAEL/LOAELs are presented in Table 3.

Table 3. Endpoints Suitable for PHG Derivation

Species	NOAEL/LOAEL	Effects	Reference
One year dog study	0.27/0.54 mg/kg	Plasma cholinesterase	ToxiGenics, 1983
Rat reproductive	0.05/0.25 mg/kg	Maternal brain acetylcholinesterase	Cambon <i>et al.</i> , 1979
Rat 60-day	0.1/0.2 mg/kg	Testicular changes/sperm abnormalities and count	Pant <i>et al.</i> , 1995
Human acute	0.05 or 0.1/0.25 mg/kg	Blood cholinesterases, clinical signs (only confirmed at 0.25 mg)	FMC, 1977

In spite of different species and types of studies, there is a remarkable congruence in that a relatively narrow range of NOAEL/LOAEL values exists. The human study (FMC, 1977) would be the most relevant for human risk determination, however, it is hampered in that a limited number of subjects were used (two). The human study is also limited because it only reported evaluations of blood cholinesterase levels and monitored clinical signs. Furthermore, none of these studies is more relevant than the others in terms of the route of administration, which for the PHG would be drinking water. Except for the dog study, in which carbofuran was administered in the diet, all of the other studies employ the bolus method of administering carbofuran directly into the digestive tract (e.g., gastric gavage). Such administration might enhance the toxicity of carbofuran, as a higher concentration of carbofuran is reaching the target tissues as opposed to a more gradual absorption of carbofuran that would be expected from ingestion of food or water.

Although inhibition of RBC cholinesterase is the most common effect seen with carbofuran exposure at lower doses, this may or may not be associated with an adverse effect. Because of the rapidly reversible nature of the inhibition, the reverse is also true: significant cholinesterase inhibition may not be found even after clear symptoms attributable to cholinesterase inhibition (Huang *et al.*, 1998; Das *et al.*, 1999). Changes in testicular morphology, although not as commonly reported, can reflect the potential for an adverse or undesirable outcome on the reproductive capacity of an organism. These changes have been reported at dose levels in the

range of blood cholinesterase inhibition. Pant *et al.* (1995) reported testicular changes of significance for risk assessment. Because this study represents the highest NOAEL with the lowest LOAEL, it has been selected as the study on which to base the PHG.

Carcinogenic Effects

There is no evidence that carbofuran is carcinogenic. Carbofuran was negative in most mutagenicity assays, regardless of metabolic activation. In some *Salmonella typhimurium* (TA 1535) (three out of 17 studies) and V-70 ouabain resistance and mouse lymphoma assays, it was weakly positive (two-fold above controls). In the chronic bioassays conducted in mice, rats, and dogs, no increase in tumor incidence was observed that could be associated with carbofuran exposure. Therefore, a carcinogenic dose-response assessment will not be conducted.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens must take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, as well as for preparing foods and beverages. It is also used for bathing or showering, and in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures. In this case, carbofuran is not volatile enough to consider inhalation as a significant exposure route for exposure by drinking water. Carbofuran is dermally permeable, however the amount potentially absorbed from brief duration household uses is marginal when compared to amount absorbed from ingestion of drinking water.

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for carbofuran in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{\text{NOAEL/LOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{L/day}}$$

where,

NOAEL/LOAEL = no-observed-adverse-effect-level or lowest-observed-adverse-effect-level,

BW = adult body weight (a default of 70 kg),

RSC = relative source contribution (a default of 20 to 80 percent),

UF = uncertainty factors (typical defaults of 10 to account for inter-species extrapolation, 10 for uncertainty from the subchronic nature of the principal study and 10 for human variability), and

L/day = adult daily water consumption rate (a default of 2 L/day).

In the Pant *et al.* (1995) study, carbofuran was administered orally to adult male rats at dose levels of 0.1, 0.2, 0.4 or 0.8 mg/kg, five days per week for 60 days. A dose-dependent decrease was observed in body weights of rats in the range of 0.2 to 0.8 mg/kg. Decreases were observed

in selected organ weights including the epididymides, seminal vesicles, ventral prostate, and coagulating glands at doses of 0.2 mg/kg and above. Decreased sperm motility, reduced epididymal sperm count along with increased morphological abnormalities of sperm (both type and number) was noted at 0.2 mg/kg and above. Significant changes were noted in various testicular enzymes including sorbitol dehydrogenase, glucose 6-P-dehydrogenase, lactate dehydrogenase and gamma glutamyl transpeptidase at doses of 0.2 mg/kg and above. The unadjusted NOAEL based on the results of this study would be 0.1 mg/kg based on absence of effects. After converting to seven days of exposure (0.1 x 5/7), the adjusted NOAEL would be 0.0714 mg/kg-day.

$$\begin{aligned}
 C &= \frac{0.0714 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{300 \times 2 \text{ L/day}} \\
 &= 0.00166 \text{ mg/L} \\
 &= 1.7 \text{ } \mu\text{g/L (rounded)}
 \end{aligned}$$

where,

$$\begin{aligned}
 \text{NOAEL} &= \text{adjusted NOAEL of } 0.0714 \text{ mg/kg-day,} \\
 \text{BW} &= 70 \text{ kg,} \\
 \text{UF} &= 300 \text{ (ten for interspecies, ten for human variability, three for} \\
 &\text{extrapolation from a subchronic study),} \\
 \text{L/day} &= 2 \text{ L/day, and} \\
 \text{RSC} &= 0.20.
 \end{aligned}$$

Use of a relative source contribution (RSC) of 0.2 in the above calculation assumes that not all of the carbofuran that is available for human exposure is from the drinking of water. Carbofuran and its metabolites have been found as residues in a number of foodstuffs. Although the exact contribution cannot be estimated, food would be the predominant avenue of carbofuran exposure to the average person.

Based on the calculated public health-protective concentration of 1.7 $\mu\text{g/L}$ (1.7 ppb), we established a PHG of 1.7 ppb for carbofuran in drinking water.

RISK CHARACTERIZATION

The primary sources of uncertainty in the development of this PHG include using uncertainty factors for inter- and intraspecies extrapolation (a factor of ten for each). The use of an interspecies factor of ten implies that humans could be more sensitive to the effects of carbofuran than was observed in the animal toxicity tests. Limited information suggests that humans are at least as sensitive as rodents and dogs to blood cholinesterase inhibition by carbofuran. From an acute toxicity study (FMC, 1977), humans exhibited early cholinergic signs at dose levels where rodents or dogs did not appear to have effects. However, cholinergic signs are sometimes difficult to detect in animals. The critical endpoint addressed in the PHG assessment, testicular toxicity, has not been noted in exposed humans nor has it been adequately evaluated. Therefore, it is not known whether humans would be more sensitive or less sensitive than rats or dogs with

regard to this endpoint. As for interindividual variation, a factor of ten is entirely appropriate for cholinesterase variations (whether RBC, plasma, or tissue). However, the extent of potential human variability in the testicular changes is unclear.

The RSC for this estimation is 0.2. This factor assumes that 20 percent of carbofuran available for human exposure comes from water sources alone. It is difficult to estimate carbofuran exposure from other sources. However, carbofuran residues have been detected in food and exposure from this route appears more likely than from drinking water, where carbofuran detection is rare. Therefore, a factor of 0.2 is used which assumes that it is more likely to be exposed to carbofuran from food than it would be from water.

Another source of uncertainty is the choice of endpoints for risk assessment. The endpoints must be both sensitive to and indicative of toxic effects from carbofuran exposure. The testicular effects, enzymatic alterations, and decreased or defective sperm output, suggest a physiological impairment. Blood cholinesterase depression (whether plasma or RBC) is an important marker of exposure and potential effects, but is neither directly associated with toxicity nor always predictable of toxicity. The testicular changes noted in the Pant *et al.* (1995) study suggest that carbofuran has the potential for impairment of reproductive function. However, it is not clear that at the doses used by Pant *et al.* (1995) that there would be a potential for cumulative toxic effects leading to more severe damage. One study (ToxiGenics, 1983) suggests that substantial injury is possible to the testes at much higher doses. Results from other chronic studies have not indicated injury to the testes, but it is more likely that this organ was not examined closely in those studies. Therefore, to address the concern over possible injury to the testes from continued dosing, an additional uncertainty factor of three was used for extrapolating effects seen with the subchronic study (Pant *et al.*, 1995).

There is no evidence that carbofuran is carcinogenic. Several chronic studies conducted in dogs, mice, and rats have not demonstrated increased tumor incidence with carbofuran treatment. Furthermore, the overwhelming preponderance of genotoxicity or mutagenicity studies suggest little potential for carbofuran to be either mutagenic or genotoxic.

OTHER GUIDANCE VALUES AND REGULATORY STANDARDS

Federal and state drinking water regulations for carbofuran in drinking water have been based on the reported effects of carbofuran in experimental animals. The federal MCLG and MCL are 0.040 mg/L for drinking water (U.S. EPA, 1995). This MCL is based on cholinesterase depression, clinical signs and testicular toxicity seen in a chronic dog study. An MCL of 0.018 mg/L was established by the California Department of Health Services (DHS), in 1995 (22 CCR 64431) based on a proposed MCL of 18 ppb (DHS, 1988). California's existing MCL differs from U.S. EPA's MCL in that it adopts the same study for MCL development as U.S. EPA, but uses a different endpoint, depression of plasma cholinesterase at a lower dose. The World Health Organization (WHO) developed a guideline of 0.007 mg/l for drinking water (WHO, 1998). This guideline was based on a NOAEL of 0.22 mg/kg-day for inhibition of red blood cell and plasma cholinesterase derived from an unpublished four-week dog study submitted to WHO.

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