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Australian Pesticides and Veterinary Medicines Authority

CARBARYL REVIEW

Part 2: Uses of carbaryl in agricultural situations

Volume 2: Toxicology and OHS report

Reconsideration of registration of products containing carbaryl and approvals of their associated labels

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ACRONYMS, ABBREVIATIONS AND DEFINITIONS

ACPH **Advisory Committee on Pesticides and Health**

ADI The **Acceptable Daily Intake** of a chemical is defined as the daily intake that, during an entire lifetime, appears to be without appreciable risk on the basis of the information available at the time of the assessment. It is expressed in milligrams of the chemical per kilogram of bodyweight (mg/kg bw). 'Without appreciable risk' means that adverse effects will not result even after a lifetime of exposure.

The determination of an ADI entails the establishment of an overall NOEL or No Observed Adverse Effect Level (NOAEL), which is generally the lowest NOEL or NOAEL in the most sensitive species. The ADI is calculated by dividing the NOEL or NOAEL by the safety factor. When based on studies in animals, the safety factor is usually 100, derived by multiplying a factor of 10 for species extrapolation with a factor of 10 for individual variation in human populations. In general terms only, a safety factor of 10 applies when appropriate human data are available. Further safety factors may have to be incorporated to provide additional protection for special risk groups (for example, infants) or where the toxicological database is of poor quality. Further safety factors may also be used when the toxicology database is incomplete (for example, in the field trial of a new chemical where it is proposed that produce from treated plants or animals be consumed) or the nature of the potential hazards indicates the need for additional caution. These supplementary safety factors may range up to 10, 20 or even 50.

APVMA The **Australian Pesticides and Veterinary Medicines Authority** is the Australian government authority responsible for the assessment and registration of pesticides and veterinary medicines, and for their regulation up to and including the point of retail sale.

ARfD The **Acute Reference Dose** is the estimated amount of a substance in food or drinking water, expressed on a bodyweight basis, that can be ingested over 24 hours or less, without appreciable health risk to the consumer on the basis of all the known facts at the time of the evaluation.

bw **Body weight**

ChE **Cholinesterase** is an enzyme of the body necessary for proper nerve function.

CI **Confidence interval**

DFR A **dislodgeable foliar residue** represents a chemical residue on the surfaces of treated foliage that is available for transfer to exposed populations (for example, workers entering treated crops) during contact with those treated leaf surfaces. That is, DFRs are the amount

	of chemical residues deposited on the leaf surface that have not been absorbed into the leaf or dissipated from the surface, and that can be dislodged.[1]
DNA	**Deoxyribonucleic acid** is a double-stranded, helical nucleic acid molecule that carries genetic information.
FAISD Handbook	The **First Aid Instructions and Safety Directions Handbook** is the *Handbook of First Aid Instructions, Safety Directions, Warning Statements and General Safety Precautions for Agricultural and Veterinary Chemicals* published by the Office of Chemical Safety in the Australian Government Department of Health and Ageing.
GLP	**Good laboratory practice**
HDPE	**High-density polyethylene** is a plastic that is resistant to many different solvents. It has a wide variety of applications, including chemical-resistant containers.
HIV	**Human immunodeficiency virus**
HPLC	**High-performance liquid chromatography** is a laboratory technique used to separate a mixture of compounds to identify, quantify and purify the components of the mixture.
JMPR	The **Joint FAO/WHO Meeting on Pesticide Residues** is an international expert scientific group that is administered jointly by the United Nations Food and Agriculture Organization (FAO) and the WHO. The JMPR is responsible for reviewing the toxicology, residues and analytical aspects of pesticides.
LC_{50}	The **median lethal concentration** is the dose of a toxicant that will kill 50% of test organisms within a designated period of time. The lower the LC_{50}, the more toxic the compound. 'LC' usually refers to a concentration of the chemical in air.
LD_{50}	The **median lethal dose** is the dose of a toxicant that will kill 50% of test organisms within a designated period of time. The lower the LD_{50}, the more toxic the compound.
LOD	**Limit of detection**
LOEL	The **Lowest Observed Effect Level** is the lowest dose of a substance to cause changes distinguishable from those observed in normal (that is, control) animals (WHO, 1990).
LOQ	**Limit of quantitation**
MOE	The **margin of exposure** is the ratio of the NOEL to the estimated exposure dose. This is the safety margin that measures the difference between the highest amount of chemical that the OCS estimates will *not* cause an adverse effect in laboratory test species, and the dosage of chemical that the OCS estimates a worker may be exposed to per day. An MOE of 100 or more, when the NOEL is based on a toxicity study in animals, is generally considered to be acceptable.

1 Gunther FA, Westlake WE, Barkley JH, Winterlin W & Langbehn L (1973). Establishing dislodgeable pesticide residues on leaf surfaces. Bulletin of Environmental Contamination and Toxicology 9(4):243–249.

MTD	**Maximum Tolerated Dose**
NHL	**non-Hodgkin lymphoma**
NHMRC	The **National Health and Medical Research Council** is Australia's peak body for funding health and medical research, providing health advice and developing ethical standards in health care and in health and medical research.
NOEL	The **No Observed Effect Level** or the No-Observable-Effect Level, is the highest dose of a substance administered to a group of experimental animals at which there is an absence of observable effects on morphology, functional capacity, growth, development or life span, which are observed or measured at higher dose levels used in the study. Dosing at the NOEL should therefore produce no biologically significant differences between the group of chemically exposed animals and an unexposed control group maintained under identical conditions. The NOEL is expressed in milligrams of chemical per kilogram of bodyweight per day (mg/kg bw/d) or, in a feeding study, in ppm in food (converted to mg/kg bw of compound intake by measured or estimated food intake over the period of the study). The NOEL has been simply defined as the highest dose of a substance that causes no changes distinguishable from those observed in normal (that is, control) animals (WHO, 1990).
OCS formerly OCSEH	The **Office of Chemical Safety** is part of the Office of Health Protection in the Australian Government Department of Health and Ageing. It is responsible for human health risk assessment policies and practices for veterinary medicines, pesticides and other environmental chemicals. It was previously known as the Office of Chemical Safety and Environmental Health. This report uses the current name.
OHS	**Occupational Health and Safety** relates to health and safety issues and actions occurring in a workplace (not domestic issues).
OR	**Odds Ratio**
PCNA	**Proliferating cell nuclear antigen**
PCO	A P**est Control Operator** is a person or company that applies pesticides as a business (for example, exterminator); the term usually describes household services, not agricultural applications.
PHED	The **Pesticide Handlers Exposure Database** is a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions, and also a set of computer algorithms used to segment and statistically summarise selected data.
POEM	The **Predictive Operator Exposure Model**, originally developed by the UK Pesticides Safety Directorate in 1996, is a model used to assess how much pesticide an operator may be exposed to through hand contamination during mixing/loading/application.
PPE	**Personal Protective Equipment** is any device or clothing worn by a worker to protect against hazards in the environment. Examples are respirators, gloves and chemical splash goggles.

ppm	**Parts per million** denotes the number of parts per 1,000,000 parts, or parts in 10^6. For example, 1 mg of impurity in 1 kg of a chemical could be expressed as 1 ppm.
RBC	A **red blood cell** is a cell that carries oxygen to all parts of the body. Also called an erythrocyte.
REI	**Re-entry Interval** is the elapsed time determined before workers can safety re-enter crops treated with a pesticide without wearing personal protective equipment.
SC	A **suspension concentrate** is a solution in which the solid active ingredient is dispersed in a liquid (normally water), together with additives, to form a stable water-dispersible suspension. Before application, the concentrate will be mixed with water to achieve the desired spraying dilution.
SUSMP formerly SUSDP	The **Standard for the Uniform Scheduling of Medicines and Poisons** contains the decisions of the National Drugs and Poisons Scheduling Committee on the classification of medicines and poisons into Schedules. The SUSMP contains certain legal requirements for the labelling of poisons and drugs that are for sale to the public. It was previously known as the Standard for Uniform Scheduling of Drugs and Poisons. This report uses the current name.
TC	The **transfer coefficient** is the area of leaf surface (cm^2) that it is estimated a worker will come in contact with in an hour of work.
US EPA	**United States Environmental Protection Agency**
WHP	The **withholding period** is the minimum period of time that must elapse between the last application of an agvet chemical product and the 'use' of the agricultural produce to which the chemical was applied.
WP	A **wettable powder** is a dry formulation that must be mixed with water or other liquid before it is applied.
WSP	**Water-soluble packaging** is a special pesticide container or package. Both the package and the pesticide dissolve when the package is dropped into water. Using pesticides in WSP helps protect the mixers from exposure to the chemical.

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1 TOXICOLOGY ASSESSMENT

1.1 Introduction

Carbaryl is a carbamate effective against a broad range of insects, mites, lice, millipedes and other pests. It is used in a diverse range of situations encompassing agricultural crops, veterinary treatment of commercial and companion animals and birds, and the home garden. Carbaryl is classified as a Schedule 6 poison in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), with Schedule 5 entries for preparations containing 10% or less of carbaryl, or when impregnated into plastic resin material containing 20% or less of carbaryl. Carbaryl preparations for human therapeutic use are listed in Schedule 4, an entry originating from the former use of carbaryl against head lice. No carbaryl-based products are now listed in the Australian Register of Therapeutic Goods.

This toxicological evaluation examines:

1. supplementary studies intended to elucidate the mechanism of tumour formation
2. replacement multi-generation reproduction and developmental studies in rats and rabbits
3. addenda to a previously evaluated developmental neurotoxicity study in rats
4. a short-term repeat-dose study and a 1-year study in dogs
5. exposure studies undertaken on persons using American registered carbaryl products in domestic settings.

During the early to mid-1990s, the sponsoring company undertook a number of studies intended to modernise the toxicological database on carbaryl, which was by then about 30 years old. Significant concerns were raised at a national and international level by findings of the oncogenic activity in mice and rats in replacement 2-year studies performed by Hamada (1993a, 1993b) at Hazleton Laboratories. These results were in contrast to the earlier carcinogenicity studies, which had proven negative.

The Office of Chemical Safety (OCS) has undertaken an evaluation of the Hamada studies, other replacement data, historical control data, and mechanistic toxicology and metabolism studies from 1994 onwards. Consideration of these evaluations by the Advisory Committee on Pesticides and Health (ACPH) occurred in October 1998. At that time the ACPH agreed with the OCS's view that there were treatment-related vascular tumours in male mice at the lowest dose tested, and reduced the Australian Acceptable Daily Intake (ADI) for carbaryl from 0.01 to 0.004 mg/kg bw/d by applying a 4000-fold safety factor to the Lowest Observed Effect Level (LOEL) of 16 mg/kg bw/d.

The OCS has also estimated the systemic doses likely to be delivered to users of Australian-registered carbaryl products, under Australian conditions. These estimates have been related to toxicological benchmarks to support recommendations on the continued registration and conditions of use of carbaryl home garden and veterinary products, including Safety Directions.

Kinetics and metabolism

Valles (1999) conducted a metabolism study in male mice that received a 50 mg/kg bw gavage dose of radiolabelled carbaryl following 14-day administration of carbaryl in the diet at 0, 10, 100, 1000 or 8000 ppm, equivalent to approximately 1.5, 15, 150 and 1200 mg/kg bw/d. Pre-treatment dose levels did not influence the excretion of radioactivity, 80% of which appeared in the urine. Up to 21 radioactive components were detected in the urine, in which the major metabolites were dihydrodihydroxy naphthyl sulfate, hydroxycarbaryl glucuronide /dihydrodihydroxy carbaryl, alpha-naphthyl sulfate and alpha-naphthyl glucuronide. Pre-treatment at 8000 ppm elicited increases in production of dihydrodihydroxy naphthyl sulfate and hydroxycarbaryl glucuronide/dihydrodihydroxy carbaryl, which are believed to be formed via epoxide intermediates. The 8000 ppm group excreted approximately 25% of the administered radioactivity in the form of these urinary metabolites, compared to 17% by the non-pretreated animals. At 8000 ppm there was also a decline in the urinary excretion of some unidentified metabolites, possibly formed by alkyl oxidation. Pre-treatment with 10 and 100 ppm carbaryl appeared to inhibit the hydrolytic pathway of metabolism. However, levels of the major hydrolysis products alpha-naphthyl sulfate and alpha-naphthyl glucuronide in the 1000 and 8000 ppm groups' urine were similar to values from the non-pretreated group, accounting for about 30% of administered radioactivity.

Short-term repeat-dose study

Hamada (1991) administered carbaryl technical to dogs in the diet at concentrations of 0, 20, 45 or 125 ppm for approximately 5 weeks. The study included measurement of plasma and red blood cell (RBC) activity before treatment and on study days 14 and 32, and brain cholinesterase (ChE) activity at termination. A probable treatment-related depression of plasma ChE activity occurred in 125 ppm males and females, which displayed up to a 23% reduction compared with baseline activity. Statistical significance against controls was achieved on day 14 but not subsequently, due mainly to a decline in ChE activity among controls. There were no treatment-related effects on RBC or brain ChE activity, or on gross necropsy findings. Consequently, the No Observed Effect Level (NOEL) is set at 45 ppm (equal to 1.4 mg/kg bw/d).

Chronic study

Hamada (1987) administered carbaryl technical to beagle dogs in the diet at concentrations of 0, 125, 400 or 1250 ppm for 12 months. Mean achieved doses were approximately 3.5, 11 and 34 mg/kg bw/d for males and 3.8, 11 and 36 mg/kg bw/d for females at 125, 400 and 1250 ppm, respectively. Bodyweight (bw) gain was inhibited to a biologically significant extent at 1250 ppm during the first 5 weeks of treatment, accompanied (in females only) by reduced feed consumption, particularly between weeks 1 and 5. Leucocyte and segmented neutrophil counts became statistically and biologically significantly elevated in 1250 ppm males.

Carbaryl caused dose-related inhibition of ChE activity at all three feeding levels in females, and at 400 and 1250 ppm in males. Plasma ChE inhibition vs control was 47–66% at 1250 ppm ($p < 0.05$ throughout the study), 9–36% at 400 ppm ($p < 0.05$ throughout the study in males and at 5, 13 and 26 weeks in females), and 12–23% in 125 ppm females ($p < 0.05$ at 5, 13 and 26 weeks). RBC ChE inhibition vs control was 30–

56% at 1250 ppm ($p < 0.05$ throughout the study) and 19–34% at 400 ppm ($p < 0.05$ at 5, 13 and 26 weeks in females but only at 5 and 13 weeks in males).

Brain ChE activity was depressed by 14–32% in the treated male groups but failed to attain statistical significance against control, while treated females showed 20–36% inhibition that was dose-related and significant ($p < 0.05$) at all doses. The female 1250 ppm group had slight but significant ($p < 0.05$) depression in albumin concentration at all measured time points, together with increased inorganic phosphorus at week 52. Absolute and relative liver weights were increased in 1250 ppm males. There were no treatment-related gross or histopathological findings. Based on statistically significant depression of plasma and brain ChE activity in females treated at the lowest dose of 125 ppm (approximately 3.8 mg/kg bw/d), the study is considered not to have demonstrated a NOEL.

Carcinogenicity studies

A subchronic carcinogenicity study was performed by Chuzel (1999) in male 'knockout' mice, heterozygous for the p53 tumour suppressor gene. The mouse strain (C57Bl/6 Tac fBR-[KO]Trp53N5-T) is phenotypically normal but has enhanced susceptibility to genotoxic events. Carbaryl was administered via the diet at concentrations of 0, 10, 30, 100, 300, 1000 or 4000 ppm (equal to 1.8, 5.2, 17.5, 52, 165 and 717 mg/kg bw/d) for 180 days. Carbaryl did not induce mortality or clinical signs. Treatment-related observations were confined to the 4000 ppm group, which displayed a slight but significant ($p < 0.01$ vs control) deficit in food consumption, correlated with lower mean bw ($p < 0.05$ or 0.01 vs control). At study termination the 4000 ppm group mean bw remained approximately 8% below the control value. A transient decrease in food consumption among the 1000 ppm group ($p < 0.05$ vs control) was not accompanied by decreased growth or bw. An increase was noted in absolute and relative liver and kidney weights at 1000 and 4000 ppm, while depression in thymus weight occurred at 4000 ppm only. Statistical significance ($p < 0.05$ or 0.01 vs control) was attained with respect to most of these parameters. Globular deposits in the upper (umbrella) cell layer of the urinary bladder epithelium affected many animals at 100 ppm or greater. The relative severity of accumulation was dose-related, but there was no accompanying irritation or hyperplastic response. The NOEL was 30 ppm (equal to 5.2 mg/kg bw/d), based on the presence of deposits in the urinary bladder epithelium at and above the next highest dose of 100 ppm. There was no treatment-related tumourigenesis.

In a study validating the use of p53 knockout mice for investigating vascular tumour development (Bigot, 1999), heterozygous (+/-) males were gavaged daily with urethane at 1, 10 or 100 mg/kg bw/d for 180 days. Seventeen/20 animals from the 100 mg/kg bw/d group died prematurely, mainly from internal haemorrhage. The entire 1 mg/kg bw/d group survived, while there were two intercurrent deaths at 10 mg/kg bw/d. Histopathology revealed hepatic angiectasis at 10 and 100 mg/kg bw/d, and vascular neoplasia in the livers of 18/20 mice receiving 100 mg/kg bw/d, together with single occurrences of hemangiosarcoma of the spleen and abdominal cavity and cardiac hemangioma. The 10 mg/kg bw/d group showed one case of multiple hepatic hemangioma. Other treatment-related tumours comprised subcutaneous sarcoma and lymphoma at 10 and 100 mg/kg bw/d, and adenoma of the lung and hepatocellular carcinoma at 100 mg/kg only. No neoplasms were present in the 1 mg/kg bw/d group. A negative control group gavaged with 250 mg/kg bw/d d-limonene displayed inappetence, mononuclear cell infiltration of the renal peripelvis and slight to moderate hyperplasia of the non-glandular stomach, but no treatment-related neoplasia. Comparison between vehicle

control groups of p53 heterozygous and wild type (p53 +/+) mice showed that the genetic difference between these strains did not affect spontaneous tumour formation.

In a published review, Venkatachalam et al. (2001) discuss the biological and molecular mechanisms underlying enhanced cancer formation in mice heterozygous for the gene coding for the p53 protein (p53+/- mice). The p53+/- mouse strain contains one wild-type allele, together with an inactive mutant gene coding for p53. Over half of the tumours collected from these mice retain an intact wild-type allele, while in the remainder the wild-type allele had become completely deleted. Tumours arising at less than 18 months of age tend to have a higher frequency of complete p53 allele loss than those arising later in the mouse life span. P53 +/- tumours that retain the wild-type allele also retain sensitivity to apoptosis following irradiation, and display other markers of p53 functionality. Compared with cells from p53 +/+ animals, fibroblasts derived from p53 -/- mouse embryos show a higher growth rate and saturation density, and less cell cycle arrest response following exposure to ionising radiation. The +/- genotype has growth characteristics and radiation response intermediate between those of the +/+ and -/- genotypes. Thus it appears that the p53 protein is 'haploinsufficient': loss of a single copy of the wild-type allele is sufficient to impair (but not prevent) the protein's tumour suppression activity. This finding is unexpected, as it has hitherto been believed that loss of *both* copies of a tumour suppressor gene are a prerequisite for tumour formation. Tumours from carcinogen-treated p53+/- mice do not reveal any consistent relationship between the carcinogen's mode of action, and whether the tumours retain or lose the remaining wild-type p53 allele. The authors suggest that the target tissue itself may have some influence over the loss or retention of the wild-type p53 allele. They conclude that carcinogenesis in the p53 +/- mouse model is likely to involve numerous carcinogen–tissue interactions that determine the likely site of tumour origin, tumour formation latency, the oncogenic lesions responsible for tumour formation, the cell-signalling pathways affected, and whether or not the wild-type p53 allele becomes inactivated.

Debruyne (1998) performed cellular proliferation studies on the kidney and liver of mice previously exposed to carbaryl for 52 weeks in a dietary study (Hamada, 1993b). Cell turnover was measured in tissue from the control and 8000 ppm interim sacrifice groups by staining for proliferating cell nuclear antigen (PCNA). The mean number of PCNA-positive renal cortical tubular cells in 8000 ppm males (3.9/1000) was approximately 3-fold higher than in control male kidney (1.2/1000). In control females, the rate of PCNA-positive hepatocytes (mean=4.6/1000) was approximately half the mean positive staining rate among the 8000 ppm group (8.3/1000). These data suggest a higher amount of cellular replication in the kidney of male mice and the liver of females receiving 8000 ppm carbaryl, compared with controls. There is an apparent correlation between this parameter and Hamada's (1993b) finding of renal and hepatic tumours in the 8000 ppm males and females, respectively. By contrast, there was no biologically significant enhancement of cell turnover in the liver of 8000 ppm males or kidney of 8000 ppm females, which were not sites of tumour development.

Irisarri (1996) measured cellular proliferation by PCNA staining in the liver, urinary bladder and thyroid gland of rats that had been exposed to carbaryl for 52 week in a dietary study (Hamada, 1993a). There was a small increase in cell cycling activity in the male thyroid and female liver at 7500 ppm. Although of equivocal biological significance, this finding does correlate with elevated incidences of thyroidal adenoma and hepatic adenoma in 7500 ppm males and females, respectively, in the chronic dietary experiment. A 10-fold increase in cell cycling in the urinary bladder epithelium of 7500 ppm males was of clear biological significance and correlates with the hyperplastic and neoplastic response observed by Hamada (1993a) within this group.

In a discussion paper, Cohen (1995) agrees with the registrant's position that carbaryl causes renal and urinary bladder tumours in rodents via a non-genotoxic mechanism. He considers it likely that the bladder tumours observed in rats at 7500 ppm resulted from a direct mitogenic effect by carbaryl or its metabolites on the urinary epithelium. Cohen's argument is based on his (1994) mechanistic study with another aromatic carbamate, propoxur, which has also been shown to cause urinary bladder cancer in rats at a high (8000 ppm) dietary dose. Cohen demonstrated cellular proliferation in the absence of necrotic injury, formation of calculi, amorphous precipitates or crystals. With regard to the proliferative lesions seen in the male rat kidney at 7500 ppm, Cohen also attributes these to mitogenic stimulus. The author concludes that without knowing the exact mechanism involved in rats, or the route of carbaryl metabolism in humans, it was impossible to predict whether cancer of the urinary tract could occur in humans. However, given that urinary tract hyperplasia and neoplasia are restricted to rats and require dietary exposure exceeding the maximum tolerated dose (MTD), such lesions are unlikely at the anticipated levels of human exposure. In this respect, Dr Cohen's conclusions are consistent with the position taken by the Australian reviewing toxicologist in the OCS's 1998 evaluation.

Reproductive studies

In a two-generation reproduction study (Tyl et al., 2001), rats were treated with carbaryl technical in their diet at concentrations of 0, 75, 300 or 1500 ppm for a 10-week period, and through mating, gestation and lactation of the resulting F1 litter. The procedure was repeated with the F1 pups, which were treated at the same doses until the end of lactation of the F2 litter. The NOEL for effects on the parental generations was 75 ppm, based on the following findings at and above the next highest dose: decreased bw gain, bw, feed consumption and conversion efficiency in F0 and F1 adults of both sexes, combined with depression in gestational bw lactational bw and feed consumption in F1 females. A single 1500 ppm F0 male was found to be producing 100% non-motile sperm that had abnormal morphology. The 1500 ppm F0 group mean sperm motility was reduced and there was a small increase in the proportion of abnormal sperm at 1500 and possibly 300 ppm. However, there were no similar findings in F1 adults. Carbaryl did not affect the sex ratio, or growth or survival of F1 or F2 foetuses *in utero*, and did not cause malformations or clinical signs among pups during lactation. However, F1 and F2 pup growth was reduced and mortality was increased during lactation at 1500 ppm. F2 pup mortality was also enhanced at 300 ppm. Puberty was significantly retarded in both sexes at 1500 ppm. The NOEL for effects on pups was therefore 75 ppm (approximately 4.7 mg/kg bw/d), based on increased mortality during lactation of the F2 litters at and above 300 ppm.

Developmental studies

Repetto-Larsay (1998) administered carbaryl by gavage to mated female rats at 0, 1, 4 or 30 mg/kg bw/d on day 6–20 inclusive of presumed gestation. No premature mortality occurred. At 30 mg/kg bw/d, most dams had at least one occurrence of increased salivation within 20 minutes of dosing, and this group also showed significantly ($p < 0.01$) depressed food consumption, a transient loss of bw at the commencement of dosing, an 8% deficit (vs control) in terminal bw, and significant ($p < 0.01$) reduction in cumulative gross and net (without uterus) bw gain. Foetal survival and sex ratio were not compromised but there was evidence of foetotoxicity at 30 mg/kg bw/d, seen as a 13% reduction in gravid uterine weight, a significant ($p < 0.01$) deficit in foetal bw, an increased incidence of runts, and delayed ossification of the spinal vertebrae and paw. However, there were no treatment-related visceral anomalies or malformations. The NOEL was 4 mg/kg

bw/d, based on maternotoxicity (salivation and depressed food consumption and bw gain) and foetotoxicity (reduced foetal bw and delayed ossification) at the highest dose of 30 mg/kg bw/d.

In a range finding study by Tyl (1999), carbaryl was administered by gavage to mated female rabbits at 0, 3, 7.5, 20, 50 or 100 mg/kg bw/d on days 6–29 inclusive of presumed gestation. No treatment-related clinical signs or unscheduled deaths were observed. There was a significant ($p < 0.05$) trend towards decreasing maternal bw gain over the dosing period, with group mean values being reduced by about 20% at 50 and 100 mg/kg bw/d. A parallel trend occurred in net maternal bw change when corrected for gravid uterine weight. At 100 mg/kg bw/d, ChE activity was inhibited by 20% in RBC and 59% in plasma ($p < 0.05$) relative to control values. There was no effect on foetal survival or development. Although a near significant ($p = 0.0506$) trend towards dose-related depression in foetal bw occurred, attributable to a 16% reduction (vs control) at 100 mg/kg bw/d, the finding was of equivocal biological significance. As this is a range finding study employing limited group sizes and limited observations, a NOEL will not be set.

Tyl, Marr and Myers (1999) gavaged mated female rabbits with 0, 5, 50 or 150 mg/kg bw/d carbaryl on day 6–29 inclusive of presumed gestation. The 150 mg/kg bw/d group lost weight over gestation day (gd) 6–9, and displayed significantly ($p < 0.01$) depressed cumulative bw gain over the dosing and entire gestation periods. When corrected for gravid uterine weight, maternal net bw loss was nearly threefold higher at 150 mg/kg bw/d than among controls. ChE activity was inhibited in relation to the dose at 50 and 150 mg/kg bw/d ($p < 0.01$). At the mid and high doses, respectively, ChE inhibition amounted to approximately 46 and 68% in plasma and 19 and 29% in erythrocytes. Treatment did not compromise foetal survival or sex ratio, but caused significant ($p < 0.01$) depression in foetal bwat 150 mg/kg bw/d. However, there were no effects on foetal development. The NOEL for maternal effects was 5 mg/kg bw/d, based on plasma and RBC ChE inhibition at and above the next highest dose of 50 mg/kg bw/d. The NOEL for foetotoxicity was 50 mg/kg bw/d, based on depressed bw at the highest dose of 150 mg/kg bw/d.

Neurotoxicity studies

In amendments to a developmental neurotoxicity study by the same authors, which was evaluated by the OCS in 1998, Robinson and Broxup (2001a, 2001b) performed additional morphometric analyses on the forebrain and cerebellum of 11- and 70-day old offspring from the control dams and dams receiving 10 mg carbaryl/kg bw/d by gavage from GD 6 to 10 days post-partum. The additional measurements had been recommended in a United States Environmental Protection Agency (US EPA) assessment which indicated a possible treatment-related decrease in the length and weight of the cerebellum in 11 day old female offspring of dams treated at 10 mg/kg bw/d, together with a bilateral increase in the width of the cerebellum in 70 day old female offspring from the same group. [The OCS's assessment did not ascribe toxicological significance to these findings because of contradictory sex- and time-related changes from control.] The findings of these two supplementary studies were entirely negative with respect to all measured parameters, and do not change the OCS's original conclusion that there were no neurotoxic or developmental effects on pups at the highest dose (10 mg carbaryl/kg bw/d). The maternal NOEL remains at 1 mg/kg bw/d (based on reduced bw gain, autonomic effects, tremors and ChE depression at the highest dose).

Human studies

A series of user exposure studies was performed, in which untrained volunteers applied various carbaryl-based home garden/veterinary insecticides while wearing a long-sleeved cotton shirt, long cotton pants and a whole body dosimeter under the outer clothing. The amount of carbaryl deposited on the clothing, inner dosimeter, hands, face and neck was measured by HPLC. Breathing zone air was also sampled and assayed for the active constituent.

During application of a 5.4% powder insecticide product to three dogs, volunteers were exposed dermally and inhalationally to a mean of 1111 and 7986 μg carbaryl, respectively, when wearing or not wearing gloves. When adjusted for volunteer bw and the amount of active constituent used, carbaryl exposure was 4.8 and 36 μg/kg bw/g applied, under the respective conditions (Merricks, 1997a).

When ungloved volunteers applied a 22.4% liquid product to vegetables, the mean exposure to carbaryl was 836 μg and 247 μg, using hose-end and hand-held pump sprayers, respectively. When adjusted for bw and the amount of active constituent used, carbaryl exposure was 0.5 and 0.4 μg/kg bw/g applied, with the respective sprayer types. If gloves were worn, total exposure was reduced to 7 μg and 5.9 μg (0.004 and 0.011 μg/kg bw/g applied), with hose-end and hand-held pump sprayers, respectively (Merricks, 1997b).

Application of the 22.4% liquid product to two large and two small trees caused volunteers to be exposed to a mean of 743 and 524 μg carbaryl when using hose-end and hand-held spray apparatus, respectively. Greater than 99% of exposure was via the ungloved hands. When normalised for bw and the amount of active constituent used, carbaryl exposure was 0.6 and 0.8 μg/kg bw/g applied, with the respective sprayer types (Merricks, 1998).

Use of a 0.1% ready-to-use liquid, which was applied directly from its pump bottle package, resulted in a mean exposure to carbaryl of 87 μg. Gloves effected a 95% reduction in dermal exposure to the active constituent. When adjusted for bw and the amount of active constituent used, carbaryl exposure was 1.2 μg/kg bw/g applied if gloves were not worn, and 0.06 μg/kg bw/g if applied with gloves (Merricks, 1997b).

When ungloved volunteers treated vegetables with a 9.8% dust product, the mean exposure to carbaryl was 1181 μg. When normalised for volunteer bw and the amount of active constituent used, carbaryl exposure was 2.1 μg/kg bw/g applied (Merricks, 1997b).

1.2 Discussion

Metabolism and toxicokinetics

The absorption, excretion and toxicokinetics of carbaryl are typical of the carbamate class. Carbaryl is extensively absorbed by the oral route and excreted rapidly in the urine by humans and experimental animals except dogs, in which the faeces is also a significant route of excretion. There is little tendency for carbaryl or its metabolites to accumulate in body tissues, even after subchronic administration. Carbaryl

induces the hepatic mixed function oxidase system in mice, showing an induction profile similar to phenobarbital.

In studies previously evaluated by the OCS, rats metabolised carbaryl by three main pathways: hydrolysis, alkyl oxidation and arene oxide formation. The latter pathway is believed to proceed via production of epoxide intermediates which are then conjugated by glutathione, either immediately or following the action of epoxide hydrase. There is some evidence (Totis, 1996) that, in rats, activity of the arene oxide/epoxidation pathway is enhanced by prolonged dietary administration of 7500 ppm carbaryl, by comparison with the pathway's activity at lower doses. There was a concomitant decline in metabolism via hydrolysis at 7500 ppm. The sponsors suggest that generation of the putative epoxides is associated with formation of kidney, urinary bladder and thyroid tumours in rats receiving 7500 ppm carbaryl during the 2-year study by Hamada (1993a). In a discussion paper, Cohen (1995) agrees with the registrant's position that epoxidised metabolites of carbaryl cause renal and urinary bladder tumours in rodents. He considers it likely that the bladder tumours observed in rats at 7500 ppm resulted from a direct mitogenic effect on the urinary epithelium, based on his (1994) mechanistic study with propoxur, which has also been shown to cause urinary bladder cancer in rats. Cohen also attributes the proliferative lesions seen in the male rat kidney at 7500 ppm to mitogenic stimulus.

In the current submission, the sponsors have directed their efforts towards finding a relationship between carbaryl metabolism and carcinogenicity in mice. In Hamada's (1993b) chronic study, vascular, renal and hepatic tumours were increased in mice treated at 8000 ppm, and vascular tumours were also elevated in 1000 and 100 ppm males. With the addition of a 10 ppm group, these same dietary carbaryl levels were administered to mice for 14 days prior to a 50 mg/kg bw oral bolus dose and subsequent quantification and identification of urinary metabolites (Valles, 1999). Consistent with results obtained in rats, pre-treatment with 8000 ppm carbaryl (but not lower doses) increased the urinary excretion of metabolites formed via epoxides, relative to products of hydrolysis and alkyl oxidation. However, the response was smaller in mice than rats. The alkyl oxidation/epoxidation pathway was not identical in the two species, giving rise to one metabolite that was unique to rats and another that was detected only in mice. This might explain the differential response of mice and rats with regard to formation of vascular or renal tumours (which were confined to mice) and neoplasms of the thyroid or urinary bladder (which occurred only in rats).

Although 10 and 100 ppm mice showed a modest decline in the proportion of carbaryl metabolised by hydrolysis, the relative activity of the hydrolysis pathway was not reduced at higher doses. Even if the finding did not arise from experimental variation, it is difficult to conceive how it would have any bearing on tumour development.

If the entire body of knowledge about carbaryl metabolism in rats and mice is considered in relationship to tumour formation in these species, some limited conclusions may be drawn, as follows:

- Arene oxide formation/epoxidation occurs in both mice and rats at all the carbaryl doses tested.
- The arene oxide/epoxidation pathway becomes relatively more active at 7500 to 8000 ppm, which exceeds the MTD in both mice and rats.

- The hydrolysis and hydroxylation pathways of carbaryl metabolism may become saturated at dietary levels exceeding 1000 ppm.
- At 8000 ppm, the occurrence of hepatic and/or vascular tumours in female mice and increased incidence of renal and/or vascular tumours among males may indeed occur in response to enhanced epoxide formation.
- Vascular tumours formed in male mice at 100 and 1000 ppm carbaryl cannot be explained in terms of preferential arene oxidation/epoxidation at 8000 ppm.
- Since the arene oxide/epoxidation pathway is also active in male mice at 10 ppm (a feeding level not tested in mouse carcinogenicity studies), the findings fail to suggest any particular threshold dose below which the formation of vascular tumours would not occur.

Overall, an association between epoxide formation and tumour development is considered biologically credible, but remains unproven. Beyond showing a difference in the epoxidised metabolites excreted by males of the two species, the metabolism studies have provided no detailed explanation as to why epoxide generation may cause vascular tumours in mice but not rats. It also remains unknown why female mice are more resistant to vascular tumour formation than males. Comparative metabolism data in female mice would have been valuable in this regard. Given that carbaryl metabolism is qualitatively similar in laboratory animals and humans, the current findings in rodents may be relevant to man, but the metabolism data alone cannot be used to predict whether humans would be more or less sensitive to vascular tumourigenesis than mice and rats.

Cholinesterase inhibition

Carbaryl possesses anticholinesterase activity typical of members of the carbamate class. In rats, ChE inhibition reaches its maximum between 0.5 and 1 hour following carbaryl administration by gavage. The subsequent time course of ChE inhibition is both dose- and tissue-/site-dependent. Recovery of plasma and RBC ChE activity is rapid (within 2 hours post-dosing at 10 mg/kg bw, and within 24 hours at 50 mg/kg bw). Brain ChE activity is slower to recover, taking 24 hours to fully regain baseline values at 10 and 50 mg/kg bw. At higher doses, reversibility is more prolonged.

ChE inhibition was the main toxicological finding in the newly submitted 12-month dog study by Hamada (1987), in which there was statistically and biologically significant inhibition of plasma and brain ChE activity at the lowest dietary level of 125 ppm (3.8 mg/kg bw/d). RBC ChE activity was inhibited at and above 400 ppm (11 mg/kg bw/d). Plasma ChE inhibition was present from week 5 onwards and persisted until termination, although the effect was diminished at weeks 26 and 52, perhaps because of a gradual reduction in achieved carbaryl dose during the study.

By contrast, when a 5-week dietary study in dogs was performed at the same laboratory 4 years later, there was no effect on brain ChE activity at the highest feeding level of 125 ppm, and the effect on plasma ChE activity, although present, probably lay near the threshold of biological significance. There were no significant methodological differences between the 5-week and 1-year studies. The delivered doses at 125 ppm in the

5-week study were very similar to those achieved during the first 5 weeks of the 1-year study. Blood samples for ChE assay were obtained about 2 hours after withdrawal of feed in both studies. It is considered that, in the 5-week study, a combination of biological variation, technical variation in the ChE assay and lack of statistical power due to small sample size (n = 6/group) may have obscured inhibition of plasma ChE at 125 ppm.

Plasma and whole blood ChE have been measured in a human study following single oral doses of up to 2.0 mg/kg bw, and at weekly intervals during administration of repeated oral doses of 0.06 or 0.13 mg/kg bw/d for 6 weeks (Wills et al., 1968). No inhibition of ChE activity was observed. However, the study is considered unreliable due to a lack of methodological detail and indications from a case report (Hayes & Laws, 1991) that acute ChE poisoning can occur in humans at 2.8 mg/kg bw.

In Table 1, NOELs are presented for plasma, erythrocyte and brain ChE activity. The data suggest that rats and dogs are more susceptible than mice to plasma ChE inhibition.

Also noteworthy is the striking disparity between NOELs demonstrated in the chronic rodent studies compared with those in the acute, 13-week and developmental neurotoxicity studies, in which the LOELs in plasma, RBC and brain were 10 mg/kg bw/d. Differences between the dosage and sampling regimes employed in the rodent 2-year and acute and repeat-dose studies are likely to be responsible. Dietary administration was used for the 2-year experiments, and the rats were probably sampled some hours after cessation of feeding, after the time of peak effect. By contrast, rats in the acute and repeat-dose studies were gavaged and then sampled 1 hour post-treatment, at the time of maximum effect. Toxicokinetic differences between dietary and oral bolus dosing may also have contributed to the apparently greater sensitivity of rats in the 13-week and developmental neurotoxicity studies.

Table 1: Summary of doses (mg/kg bw or mg/kg bw/d) at which no inhibition of ChE activity following carbaryl administration was seen

SPECIES	DURATION	PLASMA ChE	ERYTHROCYTE ChE	BRAIN ChE
Mouse	2 years	1350	16	16
Rat	Single gavage dose	Not established#	Not established#	Not established#
Rat	13 weeks	1	1	1
Rat	25 days (GD 6–LD10)	1	1	1
Rat	2 years	70	11	11
Dog	5 weeks	1.4	3.8	3.8
Dog	1 year	Not established*	3.8	Not established*

ChE inhibition occurred at the lowest dose of 10 mg/kg bw.

* ChE inhibition occurred at the lowest dose of 3.8 mg/kg bw/d.

ND = no data

Note: With the exception of the two studies in dogs, the tabulated studies have been evaluated previously and do not appear in this report.

Neurotoxicity and behavioural studies

The effects of carbaryl on the nervous system of rats, chickens, monkeys and humans are primarily related to ChE inhibition and are usually transitory. The Environmental Health Criteria Monograph on carbaryl (WHO, 1994) notes disruption to learning in rats treated for 50 days at oral doses of 10-20 mg/kg bw/d and reversible leg weakness in chickens given high doses of carbaryl but no evidence of demyelination in the brain, sciatic nerve or spinal cord sections in the birds or in long-term rodent studies. In a 10-week study in pigs, dietary administration of carbaryl at 150 mg/kg bw/d caused progressive myasthenia, incoordination ataxia, tremor, muscular contraction, terminal paraplegia and myodegeneration of the skeletal muscle. In the myelinated tracts of the cerebellum, brain stem and upper spinal cord, moderate to severe oedema was associated with vascular degeneration but no demyelination of nerve tissue was observed.

Few of the neurotoxicity studies on carbaryl that were available before 1995 appear to have been assessed in Australia. However, this situation was improved during the late 1990s by submission of a series of excellent modern studies in rats, which thoroughly characterised the test compound's effects on the central and peripheral nervous systems, ChE activity, behaviour and foetal development. Single gavage doses of 30–50 to 90–125 mg/kg bw caused overt signs of carbamate poisoning and functional deficits in behaviour together with brain, plasma and RBC ChE depression that reversed within 24 to 48 hours. ChE depression also occurred following a 10 mg/kg bw dose, but was associated only with reduced motor activity. The NOEL in the 13-week neurotoxicity study was 1 mg/kg bw/d, based on blood and brain ChE depression and behavioural effects at higher doses. A maternal NOEL of 1 mg/kg bw/d was also established on the basis of these same effects in the developmental neurotoxicity study, but carbaryl had no adverse effects on foetal or pup survival, growth or development up to and including the highest dose of 10 mg/kg bw/d. In both the subchronic and developmental studies, no adverse findings were made with respect to neuropathology in the adults or offspring.

Supplementary neurotoxicity studies were submitted for inclusion in the current review. These comprised additional morphometric measurements of the brain in offspring from rat dams treated at the highest dose in the developmental neurotoxicity study discussed above. The supplementary measurements were prompted by a US EPA assessment of that study, which was considered to have demonstrated possibly treatment-related effects on brain weight and morphology at 10 mg/kg bw/d. By contrast, the OCS evaluator attributed the findings to biological variation. The supplementary studies showed no treatment-related differences between the high dose (10 mg/kg bw/d) and control groups, and have no effect on the OCS's previous assessment.

Genotoxicity

No further genotoxicity studies have been provided since the 1998 OCS evaluation. Carbaryl has been tested *in vitro* and *in vivo* in bacterial, insect, yeast, plant and mammalian systems. Previous reviews of the genotoxic potential of carbaryl have concluded that carbaryl does not damage DNA and is unlikely to be mutagenic in humans. While carbaryl has demonstrated some clastogenic potential and activity by other

endpoints *in vitro* (mitotic recombination, gene conversion, unscheduled DNA synthesis in *Haemophilus influenzae, Bacillus subtilis, Saccharomyces cerevisiae, Aspergillus nidulans*, human lymphocytes and rat hepatocytes) at high doses that produced marked cell toxicity, it is not an *in vivo* clastogen. Carbaryl has yielded negative results in all but two mutagenicity assays in bacteria and, although several mutagenicity assays have been conducted in cultured mammalian cells, only one equivocally positive result has been obtained.

However, it would be premature to rule out the possibility that genotoxicity can be mediated by the (hypothetical) epoxides generated during carbaryl metabolism. If these entities are indeed formed in sufficient quantities, they may react with genetic material in some or all of the target tissues, under conditions that are not duplicated by the test protocols employed so far. The question will probably remain unanswered until attempts are made to detect molecular adducts on chromosomal material or other intracellular macromolecules from within the liver, kidney, thyroid, urinary bladder and hepatic/splenic vascular system of mice and rats receiving carbaryl.

Reproduction and development

One of the most significant deficiencies in the carbaryl database has been the lack of modern reproduction and developmental studies. This limitation has now been addressed with the submission of a new two-generation reproduction study in rats and developmental studies in rats and rabbits, which were performed in accordance with current good laboratory practice (GLP) standards and test guidelines.

The 1996 Joint FAO/WHO Meeting on Pesticide Residues (JMPR) observed that the (then) available reproduction studies with carbaryl were deficient by contemporary standards. In previous three-generation studies in rats, fertility was impaired and post-natal survival and growth were reduced at dietary doses > 2000 ppm (equal to 125 mg/kg bw/d) but a dose of 100 mg/kg bw/d did not induce maternal toxicity. When carbaryl was administered by gavage, maternal toxicity was not observed at 25 mg/kg bw/d but maternal toxicity, reduced litter size and reduced viability were found at 100 mg/kg bw/d. The JMPR recommended that a new two-generation study be carried out in rats, with special attention to the male reproductive system, upon which effects had been observed in some long-term toxicity studies by gavage at doses significantly lower than those evaluated in dietary studies.

The OCS was highly supportive of this recommendation, having previously evaluated a published paper (Pant et al., 1995) showing disrupted testicular morphology and spermatogenesis in Wistar rats gavaged for 90 days (5 days/week) at 50 or 100 mg/kg bw/d. Pant et al. observed testicular congestion and oedema, moderate atrophy of the seminiferous tubules, an approximately twofold increase in the proportion of abnormal sperm and a 40% reduction in sperm count vs control at 50 mg/kg bw/d. At 100 mg/kg bw/d, testicular congestion and oedema were more intense, masses were present within the seminiferous tubules, the proportion of abnormal sperm was trebled and sperm count was depressed by 60%. There were dose-related depressions in glucose 6-phosphate and sorbitol dehydrogenase activity and elevations in LDH and GGT activity. The findings of Pant et al. are not isolated. Vashakidze (1975; evaluated by WHO in EHC 153 [1994]) reported decreased sperm motility and increased sperm abnormalities in rats intubated orally with carbaryl for 1 month at doses of 5 mg/kg bw/d or greater.

The current two-generation reproduction study (Tyl et al., 2001) found possible treatment-related effects on the male reproductive system at the highest dose of 1500 ppm (approximately 97 mg/kg bw/d). A single F0 adult male was found to be producing 100% non-motile sperm that lacked tails. The finding was not correlated with reproductive failure, however, as the animal had mated and conceived a litter of viable pups. Given that 3 weeks had elapsed between mating and sacrifice of the F0 males, complete loss of active sperm may have not developed until the post-mating period. There was also an apparent dose-related increase in the percentage of abnormal sperm seen in the 1500 and 300 ppm F0 males, but it was not repeated in the F1 generation.

Differences in dosing methods may explain the variation between the outcome of the studies by Tyl et al. and Pant et al. The 1500 ppm males in the study of Tyl et al. received carbaryl by dietary administration; whereas Pant et al. administered carbaryl orally in peanut oil (the exact technique was not described). Oral absorption of carbaryl is rapid, suggesting that higher peak blood and tissue levels may be attained after bolus dosing than following dietary intake of an equivalent dose over the usual 8-hour rodent feeding period. There may also be genetic differences in susceptibility between the Wistar rats used by Pant et al. and the CD (Sprague-Dawley) strain used by Tyl et al. Unfortunately, there is insufficient information available on the study by Vashakidze (1975) to enable comparison between the test material, animals and methods used by that author and Tyl et al.

The delayed puberty in F1 pups and reduced anogenital distance at birth in F2 males at 1500 ppm raise the question as to whether carbaryl mediates a specific effect on sexual development. However, the study's findings do not support such a hypothesis. Anogenital distance was found to be dependent on pup birth weight (that is, smaller male pups tended to have shorter anogenital distance) and hence is unlikely to have been reduced by feminised sexual development of male foetuses. Puberty was retarded in both sexes (which provides further evidence against a gender-specific effect) and retardation occurred only in the presence of inhibited bw gain. These findings are therefore both considered to be secondary to effects on bw and bw gain.

In the developmental studies, maternotoxicity was seen as cholinergic signs in rats, inhibition of plasma and RBC ChE activity in rabbits, and depressed weight gain in both species. Foetal development was retarded at maternally toxic doses, but there were no treatment-related visceral anomalies or malformations. The results were broadly consistent with those of studies previously evaluated by the OCS and the JMPR.

Carcinogenicity

Carbaryl is remarkable for its carcinogenic activity in the chronic rodent studies by Hamada (1993a, 1993b), having caused tumours of the thyroid, urinary bladder and liver in rats, and kidney, liver and vascular system in mice. In the current submission, cell cycling studies on tissue specimens from Hamada's studies (with the exception of sites of vascular tumour formation) demonstrated enhanced cellular division in target tissues. These results were in marked contrast to negative findings in a series of previous oncogenicity studies in both species, dating to the early 1960s.

However, with the exception of vascular tumours, carcinogenicity did not occur below the highest doses administered (8000 and 7500 ppm in diet to mice and rats, respectively). In many respects, the high-dose tumours are suggestive of inappropriate study design. On a daily basis, the high-dose groups received equivalent to or greater than the acute oral median lethal dose (LD_{50}), and displayed marked systemic toxicity including depressed weight gain and feed consumption, behavioural changes, cataracts and anaemia. Thus, the 7500 and 8000 ppm groups were treated at above the MTD. Since carbaryl has not shown any convincing evidence of genotoxic activity, and because NOELs of 1000 and 1500 ppm were demonstrated in the respective species for bladder, hepatic, thyroid and renal tumours, neither the OCS nor the ACPH has regarded these high-dose tumours as a barrier to continuing registration of carbaryl, subject to adequate safeguards that would limit public exposure to the chemical.

From a regulatory standpoint, the vascular tumours are of significantly greater concern. Although these did not develop in female mice at below the 8000 ppm feeding level, there was no apparent NOEL in males, even at the lowest dose of 100 ppm (equivalent to approximately 16 mg/kg bw/d). In the opinion of the OCS, ACPH and JMPR, historical control data on the incidence of vascular tumours have failed to demonstrate that Hamada's findings were attributable to biological variation. Furthermore, while there are often fairly well established non-genotoxic modes of action underlying the development of liver, thyroid, kidney and urinary bladder tumours in rodents, vascular hemangioma and hemangiosarcoma are more difficult to explain, and their human relevance cannot be dismissed.

The sponsors have now focused on eliminating genotoxicity as a probable mode of action for carbaryl. This has been attempted by use of a novel short term carcinogenicity bioassay in male p53 'knockout' mice, which compared tumour development among animals treated with carbaryl, d-limonene (as a negative control) and urethane (as a positive control).

The function of the p53 gene is related to regulation of the cell cycle. Cellular levels of p53, a phosphoprotein transcription factor, are greatly increased by radiation and other DNA-damaging agents, and this increase in p53 is accompanied by an arrest in late G1 of the cell cycle. Wild type p53 can also mediate apoptosis (Donehower, 1996). By contrast, cells in which the p53 gene is deficient may continue to replicate while incorporating genetic errors that would normally be repaired or excised. Many types of human tumours contain mutations and loss of the p53 gene. In addition, germ line mutations in p53 have been identified in affected individuals of Li-Fraumeni syndrome families, who have a 50% likelihood of developing cancer by the age of 30 (Donehower, 1996).

The heterozygous p53-deficient mice used in the current oncogenicity study with carbaryl are phenotypically normal but have enhanced susceptibility to genotoxic events, both spontaneous and induced. The pattern of spontaneous tumour formation among p53 heterozygous mice is of major importance to their utility in the investigation of vascular tumours. Less than 8% of these mice develop tumours before 9 months of age, but tumour incidence subsequently increases to 50% by 18 months and 90% by 2 years. The principal spontaneous neoplasia in p53 +/- animals are soft tissue sarcomas, osteosarcomas and lymphomas (approximately 30% incidence, each), with brain tumours and unspecified carcinomas accounting for the remainder (Donehower, 1996). Vascular hemangiomas and hemangiosarcomas are uncommon, which does enhance the biological significance of their formation when p53 knockout mice are treated with xenobiotics.

Donehower (1996) notes accelerated development of liver hemangiosarcoma in dimethyl nitrosamine-treated p53 +/- mice, while in the current study in p53 knockout mice, vascular tumours were induced by the genotoxic carcinogen urethane (Bigot, 1999). It is of interest that urethane is metabolised to vinyl carbamate, which is further metabolised to the ultimate carcinogen, vinyl carbamate epoxide. Vinyl carbamate epoxide reacts with DNA to form one minor and two major adducts, giving rise to an A to T transversion mutation (Bowden, 1997).

Detoxification of epoxides is essential for cell survival and depends mainly on the action of epoxide hydrase or glutathione transferase. Hayes (1994) notes the existence of two forms of epoxide hydrase, an endoplasmic reticular form highly active in adult rats (especially males), and a cell cytosol form that is more active in mice than rats. Perhaps sensitivity to vascular tumour formation can be influenced by species- and gender-specific differences in epoxide hydrase activity. Circumstances leading to glutathione depletion may also enhance the vulnerability of target cells to electrophilic injury.

No treatment-related tumourigenesis occurred in p53 heterozygous mice treated with d-limonene, a non-genotoxic renal carcinogen in male rats that acts by causing α_{2U}-globulin accumulation. Nor did carbaryl elicit tumourigenesis, at up to the highest dietary feeding level of 4000 ppm.

Taken at face value, the negative findings with carbaryl in p53-deficient mice provide support for the view that carbaryl need not be regulated as a genotoxic carcinogen. Nevertheless, any chemical metabolised via a reactive electrophile must be viewed with concern.

Despite the knowledge gained from the current studies, there are still limitations in our understanding of carbaryl's carcinogenic properties, and its mode or mechanism(s) of action remain uncharacterised. The submitted cell cycling studies did not examine vascular tissue. There is a lack of regulatory experience with p53 knockout mouse carcinogenicity studies, which is sufficient to prevent the OCS from discounting the results obtained in Hamada's (1993a) conventional 2-year experiment. There is also no indication as to which of the three modern carcinogenicity bioassays with carbaryl (6-month 'knockout' mouse, 2-year mouse or 2-year rat) has the most human relevance. Under the circumstances, the reviewer considers that the OCS should continue to uphold use of an enhanced safety factor and reduce public exposure to the lowest extent reasonably achievable.

Human studies

So far, there is no evidence that carbaryl is carcinogenic in humans. An epidemiology study of workers employed at a United States plant that produces carbaryl showed a slightly lower overall rate of mortality from cancer than expected from the general population. Although there was an excess of brain tumours, this lay well within the range of chance and cannot be attributed to exposure to carbaryl.

The current submission included human exposure studies that measured the amount of carbaryl deposited on the skin and clothing of volunteers who were using American carbaryl products in simulated home garden and home veterinary situations. The concentration of carbaryl in their breathing zone air was also measured. The studies were noteworthy for their good design and clear description of the activities performed by the

volunteers, and yielded detailed data on the extent and pattern of carbaryl exposure, the amount of inter-individual variation in exposure, and the effectiveness of gloves and clothing in reducing exposure.

The product that had by far the greatest potential for human exposure was a 5% carbaryl veterinary dusting powder. Then, in decreasing order of exposure potential, were 10% vegetable dusts, a 22% liquid concentrate applied to vegetables or trees by spray, and a 0.1% ready-to-use vegetable spray. In all cases, the majority of exposure occurred via the hands. The veterinary dusting powder also caused significant exposure by inhalation whereas inhalation exposure by vegetable dusting and application of carbaryl sprays was negligible. In general, only about 5% or less of carbaryl that became deposited on the external clothing penetrated to the skin, and comparison between gloved and un-gloved subjects showed that gloves effected a 95% reduction in exposure to the active constituent.

There was wide inter-individual variability in the extent of exposure to carbaryl after using the same product for the same application. For example, after applying insecticidal dust to dogs, the most carbaryl found on a volunteer's internal dosimeter was 13,153 μg, compared with a minimum of 63 μg. When spraying vegetables without gloves, the lowest and highest carbaryl loads on the hands were 63 and 4,440 μg, respectively. This occurred despite all members of the study group performing standardised tasks under supervision, which would have prevented them from preparing grossly over- or under-strength spray mixtures, or mis-applying the various products.

NOEL considerations

A summary of the NOELs determined for carbaryl is shown in Table 2. Note that the table omits studies that have not been evaluated by the OCS, are unsuitable for regulatory purposes, or have been superseded by replacement data.

Table 2: Summary of the NOELs determined for carbaryl

STUDY	NOEL (mg/kg BW/D)	LOEL AND TOXIC EFFECTS
Dogs: 5-week dietary	1.4	3.8 mg/kg bw/d: depressed plasma ChE activity
Mice: 6-month dietary	5.2	17.5 mg/kg bw/d: deposits in urinary bladder epithelium
Mice: 2-year dietary	Not established	16 mg/kg bw/d: vascular system tumours in males
Rats: 2-year dietary	11	70 mg/kg bw/d: depressed bw gain and brain and RBC ChE activity
Dogs: 1-year dietary	Not established	3.8 mg/kg bw/d: depressed plasma and brain ChE activity
Rats: 2-generation dietary reproduction	4.7	19 mg/kg bw/d: decreased parental bw gain, bw, feed consumption and conversion together with increased pup mortality during lactation
Rats (male): 90-day reproduction by gavage	Not established	50 mg/kg bw/d: lethargy, decreased bw gain and spermatogenesis, increased testicular LDH and GGT activity, testicular atrophy
Mice: dietary developmental	No adverse effects at highest dose of 30 mg/kg bw/d	–
Rats: developmental by gavage	4.0 for both maternal and foetal effects	30 mg/kg bw/d: salivation, depressed feed consumption and bw gain in dams; reduced bw and delayed ossification in foetuses
Guinea pigs: developmental by gavage and dietary administration	No treatment-related effects at highest doses of 200 mg/kg bw/d (gavage) or 300 mg/kg bw/d (dietary)	–
Rabbits: developmental by gavage	5.0 for maternal effects 50 for foetal effects	Does: 50 mg/kg bw/d: plasma and RBC ChE inhibition Foetuses: 150 mg/kg bw/d: depressed bw
Dogs: dietary developmental	3.1 for foetal effects No maternal effects at highest dose of 50 mg/kg bw/d	Pups: 6.3 mg/kg bw/d: skeletal and visceral abnormalities in the absence of maternal toxicity
Rats: 13-week neurotoxicity by gavage	1.0	10 mg/kg bw/d: blood and brain ChE inhibition and reduced motor activity
Rats: developmental neurotoxicity by gavage	for maternal effects No adverse effects on pups	10 mg/kg bw/d: decreased maternal bw gain, ataxia, gait disturbance, tremor, constricted pupils, inhibited plasma, RBC and whole blood ChE activity

1.3 Committee considerations

National Drugs and Poisons Schedule Committee

The Poisons Schedule status of carbaryl was considered by the National Drugs and Poisons Schedule Committee at its 36th meeting (15–17 October 2002). The committee noted that removal of the Schedule 4 entry had been recommended by the then Chemical Review and International Harmonisation section on the basis that carbaryl was carcinogenic in experimental animals; the available data did not permit an adequate risk assessment to be undertaken in relation to the treatment of head lice and there were no registered human therapeutic products containing carbaryl.

However, the Committee considered that:

- Removal of carbaryl from Schedule 4 would delete an important import control over therapeutic goods for human use containing carbaryl, that is, the need for a prescription and the agreement of a physician to the proposed use.
- Likewise removal from Schedule 4 would permit a pharmacist to include carbaryl in a compounded preparation for individual use.
- Under the Trans-Tasman Harmonisation guidelines agreed by the committee, where both New Zealand and Australia had no registered products, the entry would be retained until the completion of retrospective harmonisation. At this time, the retention or removal of these entries would be considered on their merits.
- Inclusion in Appendix C was not supported as New Zealand had no equivalent and would still have to retain carbaryl in Schedule 4, and it was debatable whether the toxicity profile warranted inclusion in Appendix C.
- Members supported the retention of the Schedule 4 entry to foster harmonisation with New Zealand and to maintain existing controls over imports and dispensing by pharmacists.

The outcome of the committee's consideration was that:

- The existing scheduling for agricultural and veterinary uses of carbaryl was appropriate on the basis that the toxicity profile as confirmed as appropriate for inclusion in Schedule 6, and Schedule 5 for preparations containing 10% or less of carbaryl.
- The removal of the Schedule 4 entry was not supported on the basis that a doctor's prescription should continue to be required for any human therapeutic use of carbaryl.

Advisory Committee on Pesticides and Health

The 20th meeting of the ACPH (19 October 2000) was invited to comment upon the OCS's review of the latest data, in particular the following:

- the utility of short-term carcinogenicity studies in p53-deficient mice, both with respect to carbaryl and more generally
- in light of the negative findings in the short-term carcinogenicity study with carbaryl, was there any justification for changing the 4000-fold safety factor upon which the ADI is currently based?
- the OCS's recommended Acute Reference Dose (ARfD) for carbaryl
- a toxicologically defensible systemic dose of carbaryl to which persons may be exposed when using carbaryl products within the home
- the assumptions used in estimating the systemic doses of carbaryl that would be absorbed by persons using or making contact with carbaryl within the home garden/veterinary setting
- whether the OCS's recommendations with respect to continued registration of home garden and home veterinary products are justified
- whether any further exposure scenarios should be considered
- whether the human exposure model developed by the OCS was applicable to other home garden and home veterinary pesticides.

Carbaryl was considered again by the ACPH at its 23rd meeting (2 May 2002), in particular:

- the OCS's review of additional toxicology studies on carbaryl, which had strengthened the overall database (particularly in terms of repeat-dose and chronic toxicity in non-rodents, and reproductive toxicity) but not advanced the state of knowledge on the carcinogenicity of carbaryl in rodents and its relevance to humans
- the JMPR's ARfD of 0.2 mg/kg bw for carbaryl, applying a 25-fold safety factor to a NOEL for anticholinesterase effects of 3.8 mg/kg bw/d in a 5-week dog study
- the JMPR's reduction of the safety factor applied to the 16 mg/kg bw/d LOEL for tumour formation in male mice from 5000-fold to 2000-fold, resulting in an increase in the JMPR ADI for carbaryl from 0.003 to 0.008 mg/kg bw/d. The reduction in the safety factor appeared to have been made in light of the absence of carcinogenic activity in the 6-mo carcinogenicity study with carbaryl in p53 'knockout' mice, together with other supporting evidence that carbaryl is not a genotoxic carcinogen.

The OCS proposed an Australian ARfD of 0.01 mg carbaryl/kg bw, based on the NOEL for ChE inhibition and behavioural disturbance of 1 mg/kg bw/d in 13-week and developmental neurotoxicity studies in rats. There is no reliable NOEL for anticholinesterase effects in humans, noting that humans have shown clinical signs of anticholinesterase toxicity at carbaryl doses as low as 2.8 mg/kg bw po, which lies below the canine short-term NOEL for RBC and brain ChE inhibition. The proposed ARfD of 0.01 carbaryl/kg bw was accepted.

The OCS also sought the opinion of the ACPH as to whether there was any justification for the safety factor applied to the pivotal LOEL for tumour formation in male mice to be revised from its current value of 4000.

1.4 Determination of public health standards

Acceptable Daily Intake

In October 1998 the ACPH reconsidered the ADI for carbaryl, in light of the expanded toxicological database then available, and the draft National Health and Medical Research Council (NHMRC 1999) guidelines for derivation of modifying factors for seriousness of carcinogenic effect. The ACPH recommended that a 4000-fold safety factor be applied to the LOEL of 100 ppm (16 mg/kg bw/d) for vascular tumours in male mice in a 2-year dietary study, giving a revised ADI of 0.004 mg/kg bw/d.

At its October 2000 meeting, the ACPH reconsidered the ADI for carbaryl in light of the reviewed carcinogenicity study in p53 'knockout' mice and supplementary studies on the mechanism of tumour formation. The committee confirmed that the continued use of the 4000-fold safety factor for deriving the ADI remained appropriate given the continuing limitations in understanding carbaryl's carcinogenicity in rodents. No new data relevant to the carcinogenicity of carbaryl have subsequently become available. Furthermore, none of the additional studies evaluated in this report is considered to be a more suitable basis for the ADI than the current pivotal 2-year study in mice.

However, the OCS notes that following the JMPR-2001 consideration of the carcinogenicity study with carbaryl in p53 'knockout' mice, the JMPR ADI for carbaryl has been increased from 0.003 to 0.008 mg/kg bw/d. This was brought about by reducing the safety factor applied to the 100 ppm LOEL for vascular tumourigenesis, from 5000- to 2000-fold. Furthermore, comment received from Bayer CropScience (formerly Aventis) on the (June 2002) draft of the Australian review has highlighted the conservatism of Australia's 4000-fold safety factor, particularly in light of the negative result obtained with carbaryl in the study in p53-deficient mice.

Taking all relevant factors into consideration, the OCS agrees that the negative result obtained in the 6-month study in p53-deficient mice has indeed significantly increased the weight of evidence that carbaryl is not genotoxic *in vivo*, thereby reducing concern over potential effects on human health. This enables the component for 'confidence that carbaryl is genotoxic' to be reduced from 2 to 1, and using the NHMRC criteria on deriving safety factors, the effect of the modification is to reduce the overall safety factor from 4000 to 2000. Application of the 2000-fold safety factor to the LOEL of 100 ppm (16 mg/kg bw/d) for vascular tumours in male mice yields a revised ADI value of 0.008 mg/kg bw/d.

This approach yields the same outcome as the conventional method of deriving safety factors for agricultural and veterinary chemicals, which would incorporate the standard 100-fold component (10 for extrapolation from animals to humans X 10 for variation in sensitivity within the human population), together with an additional 10-fold factor for the use of a LOEL instead of a NOEL, and an extra 2-fold factor allowing for the remaining uncertainty as to the mode and mechanism of vascular tumour formation and for the impossibility of discounting the relevance of vascular tumours to humans.

Given that the LOEL for vascular tumour formation is probably near the threshold dose for tumourigenesis in mice, a margin of greater than 2000-fold between the ADI and the LOEL would not be likely to increase human safety. Hence, a 2000-fold safety factor should be sufficient to prevent a carcinogenic hazard to humans from dietary intake.

Acute Reference Dose

At the start of the review an Australian ARfD value for carbaryl had not been set. Among the toxicological studies that would possibly be a suitable basis for an ARfD, the lowest NOEL is 0.06 mg/kg bw/d, established in a 6-week oral study performed in male prisoners (Wills et al., 1968). An increased urinary amino acid:creatinine ratio was observed at the next highest dose of 0.12 mg/kg bw/d, and was interpreted by the JMPR (1970) as a slight decrease in the ability of the proximal convoluted tubule to re-absorb amino acids. Plasma and whole blood ChE activity was unaffected at either dose. Clinical signs or effects on ChE activity were not observed in a preliminary range-finding experiment, in which pairs of prisoners received single oral doses of up to 2 mg/kg bw carbaryl. However, the study's authors failed to specify the time interval that elapsed between dosing and blood sampling during the main and range-finding experiments. It is therefore possible that undetected ChE inhibition occurred, given that ChE activity recovers rapidly following inhibition by carbaryl. Although the prison pharmacist checked the subjects' mouths after dosing to ensure the capsules had been swallowed, there must also be some uncertainty as to whether the carbaryl was indeed taken as intended by the study authors. Given these uncertainties, the Wills et al. study is considered unsuitable for regulatory purposes.

Two case studies of adverse effects in humans following carbaryl ingestion are reported in the *Handbook of Pesticide Toxicology* (Hayes & Laws, 1991). A scientist exploring the possible value of carbaryl as an anthelmintic ingested 250 mg (approximately 2.8 mg/kg bw). After 20 minutes, he suddenly experienced violent epigastric pain, and a little later he began to sweat profusely. A 1 mg dose of atropine produced little improvement. He gradually developed great lassitude and vomited twice. One hour after taking the carbaryl, and after a total atropine dose of 3 mg, he felt better, and was completely recovered after 2 hours. In the second incident, a scientist ingested (on an empty stomach) a suspension containing about 420 mg carbaryl (approximately 5.5 mg/kg bw). (He had previously taken larger doses about 1 hour after a meal without any resulting illness.) After 85 minutes, he noted a slight change in vision and after 90 minutes he began to feel nauseated and lightheaded. Two mg atropine provided relief but the symptoms returned. The atropine dose was increased to 4.8 mg. Despite this, the nausea persisted and profound weakness, profuse sweating and hyperperistalsis developed. The symptoms attained maximum severity about 2 hours after their onset, but definite improvement occurred within 3 hours of onset and recovery was nearly complete after 4 hours.

Two additional studies in humans are briefly summarised in the review of carbaryl by the International Program of Chemical Safety. Both studies (Hansen, 1978; Ward et al., 1988) were investigations of carbaryl metabolism and involved administration of oral doses of up to 1 mg/kg bw. No mention was made of any clinical signs or other treatment-related effects in the subjects. Although suitable data on RBC ChE activity in humans could be used for setting an ARfD for carbamates or organophosphates, the study of Wills et al. is considered unreliable, and there are no other data that would establish NOELs or LOELs for ChE inhibition by carbaryl in humans. The ARfD for carbaryl therefore has to be based upon studies in experimental animals.

A series of acute dose rangefinding studies was performed in unfasted rats gavaged with carbaryl at 10 mg/kg bw and above. The 10 mg/kg bw dose did not cause clinical signs but elicited a transient 40% decrease in motor activity (in males) at 1 hour post-treatment, together with a 1°C depression in body temperature (in females). Plasma and RBC ChE activity were depressed by up to approximately 30%. Brain ChE activity was inhibited by 30–50%.

The 1-year dog study evaluated here did not demonstrate a NOEL, due to brain and plasma ChE inhibition at the lowest dietary dose of 3.8 mg/kg bw/d. RBC ChE activity was not affected at that dose, but was inhibited at and above 11 mg/kg bw/d. Despite these findings, clinical signs did not occur even at the highest dose of 34 mg/kg bw/d. The 5-week dog study found no effect on RBC or brain ChE activity at the highest dose of 3.8 mg/kg bw/d, and formed the basis of the ARfD set by the JMPR in 2001. In 1996, the JMPR summarised the Hayes and Laws case report in humans in which clinical signs were observed at 2.8 mg/kg bw. However, in the 2001 report there was no comment about this observation. Given that overt toxicity in humans occurs *below* the NOEL for RBC and brain ChE inhibition in dogs, dogs must be significantly more resistant to the effects of carbaryl than humans. In the absence of comparative data on the toxicokinetic and toxicodynamic behaviour of carbaryl in dogs and humans, there is no explanation for the interspecies difference in sensitivity. Hence, the OCS concluded that the NOEL in the 5-week dog study can not be used as a basis for the ARfD because it corresponds to an effect level in humans.

The lowest NOEL in repeat-dose studies in animals that is also not associated with clinical signs in humans is 1 mg/kg bw/d, established in rat 13-week subchronic and developmental neurotoxicity studies, based on behavioural indications of autonomic neurotoxicity and brain, plasma and erythrocyte ChE depression (LOEL = 10 mg/kg bw/d). Application of a 100-fold safety factor to the 1 mg/kg bw/d NOEL would yield an ARfD of 0.01 mg/kg bw. This is in contrast to the ARfD set by the JMPR of 0.2 mg/kg bw.

Intake from drinking water

Current registered uses of carbaryl include cotton and rice. Where a pesticide is registered for use in water or water catchment areas, the Joint Committee of the Agricultural and Resource Management Council of Australia and New Zealand and the NHMRC set Guideline and Health Values for the chemical in drinking water. A Guideline Value is generally based on the analytical limit of determination, and is set at a level consistent with good water management practice and that would not result in any significant risk to the consumer over a lifetime of consumption. Exceeding the Guideline Value indicates undesirable contamination of drinking water and should trigger action to identify the source of contamination and prevent further contamination. However, a breach of the Guideline Value does not necessarily indicate a hazard to public health. The current Guideline Value for carbaryl is 0.005 mg/L.

Health Values are intended for use by health authorities in managing the health risks associated with inadvertent exposure such as a spill or misuse of a pesticide. The values are derived to limit intake *from water alone* to about 10% of the ADI, on the assumption that (based on current knowledge) there will be no significant risk to health for an adult weighing 70 kg at a daily water consumption of 2 L over a lifetime. At present, the Health Value for carbaryl is 0.03 mg/L (*Australian Drinking Water Guidelines: Summary*, NHMRC, Canberra, Australia,1996; ISBN 0 642 24462 6; http://www.nhmrc.gov.au/publications/pdf/eh20.pdf).

Given that the ADI for carbaryl is 0.008 mg/kg bw/d, the Health Value may be calculated as:

0.008 mg/kg bw/d x 70 kg x 0.1

2 L/d

= 0.028 mg/L

Hence, the current Health Value for carbaryl of 0.03 mg/L is supported, and no revision is proposed.

Public exposure

Carbaryl is used for the control of a diverse range of insect pests on animals and edible and ornamental plants, and is also effective against other arthropods, including millipedes, when applied to and around buildings. Public exposure to carbaryl is therefore expected to occur from:

- consumption of residue in commercially treated fruit, vegetables and other commodities
- consumption of residue in home-grown fruit and vegetables
- dermal and inhalational exposure when preparing and/or using home garden and home veterinary products
- dermal contact with pets, carpets, lawns and exterior surfaces treated with home garden or home veterinary products
- dermal contact with surfaces treated by pest control operators (PCOs).

Public exposure to home garden and home veterinary products is discussed at length in *Carbaryl Final Review Report and Regulatory Decision: Part 1 (Home garden, home veterinary and domestic situations)* and will not be repeated here.

Post-application exposure

The use of some carbaryl-based home garden and professional products inside domestic homes, on lawns and as a chemical barrier on paths and walls brings with it the question of occupants' exposure from treated surfaces. In the absence of relevant experimental data, the OCS has relied upon US EPA default factors for estimating the transfer of carbaryl from turf and hard surfaces, in conjunction with the application rate per unit area calculated from the product label instructions.

Sitting or lying on treated grass or walking barefoot on treated paving could deliver systemic doses above the ADI and ARfD if the carbaryl was not washed off the contaminated skin within an hour. Here, the OCS recommends that the appropriate risk reduction strategy is to direct householders to keep off treated surfaces.

The indoor use of carbaryl is more problematic. The OCS has no data on the persistence of carbaryl indoors. Noting that household residents (especially infants) are more likely to make contact with a treated floor than grass or pathways, and that ChE depression has been recorded in persons whose residences have been treated indoors with carbaryl (WHO, 1994), the OCS believes that label warnings are insufficient to ensure safety. Consequently, it is recommending that carbaryl should not be registered for indoor use.

The APVMA has determined that the labels of all carbaryl products should be varied to rule out internal domestic use and to instruct users that bare skin contact with treated surfaces should be avoided for 7 days.

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2 OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

2.1 Introduction

Carbaryl is a carbamate effective against a broad range of insects, mites, lice, millipedes and other pests. It has been used in a diverse range of situations encompassing agricultural crops, veterinary treatment of commercial and companion animals and birds, and the home garden. This occupational health and safety (OHS) review covers carbaryl-based professional use products, and is based on the following sources: product user exposure studies and foliar residue studies submitted by the registrants, published studies, product labels, and the OCS toxicology review of 2004.

2.2 Professional use carbaryl products

Six carbaryl products for professional use are covered in this assessment. Two are veterinary products while the remainder are intended for use by the professional agricultural and pest control sectors. These products are shown in Table 4 below.

Table 4: Six products considered in the occupational health and safety assessment for the review of carbaryl

APVMA PRODUCT CODE	PRODUCT NAME	DESCRIPTION	CARBARYL CONTENT
32009	Nufarm Flowable Carbaryl 500 Insecticide	SC; S6; Control of pests in agricultural, industrial and domestic settings	500 g/L
40143	Joseph Lyddy G-Wizz Insecticidal Dry Shampoo for Horses and Ponies	Soap bar; S5; Control of ectoparasites	37 g/kg
40145	Joseph Lyddy Y-Itch Animal Insecticide Bactericide	Shampoo; S5; Control of ectoparasites	2.0 g/L
40146	Bugmaster Flowable Insecticide	SC; S6; Control of pests in agricultural, industrial and domestic settings	500 g/L
49326	Kendon Carbaryl Wettable Powder Insecticide	WP; S6; Control of pests in agricultural, industrial and domestic settings	800 g/kg
52213	David Grays Carbaryl 500 Flowable Insecticide	SC; S6; Control of pests in agricultural, industrial and domestic settings	500 g/L

800 g/kg wettable powder

Kendon Carbaryl Wettable Powder Insecticide is available in 1, 10 and 25 kg packs and is intended for control of insects in a variety of agricultural situations and control of millipedes around buildings and in garden areas. Application is by spray, but no particular apparatus is specified. Users are instructed to pre-

mix the required quantity of the powder with sufficient water to form a thin cream before adding it to the half-full spray tank under agitation. The remainder of the water is then added. Empty containers (design unknown) are single-rinsed before disposal.

Uses on trees:

- avocados, on young trees and at flowering against monolepta beetles, at 130 g product/100 L (1 g carbaryl/L)
- duboisia, against moths, caterpillars, beetles and locusts, 130 g product/100 L (1 g carbaryl/L)
- macadamias, applied in spring and autumn against twig girdlers and monolepta beetles, or 4 times onto the nut clusters at 2–3-week intervals against nut borers, at 130 g product/100 L (1 g carbaryl/L)
- ornamentals, at 130 g product/100 L (1 g carbaryl/L)
- pome fruit, applied for fruit thinning 7–28 days after full bloom at 100–130 g product/100 L (0.8–1 g carbaryl/L)
- stone fruit, applied by jet or coarse spray to the trunks and limbs when attacked by fruit tree borers, at 180 g product/100 L (1.4 g carbaryl/L)
- elms, against leaf beetles, applied as a band around the trunk at a height of at least 1.5 m, at 2.5 kg product/100 L (20 g carbaryl/L). Alternatively, small trees may be treated by foliar spray at 125 g product/100 L (1 g carbaryl/L).

Cereals (maize and sorghum) may be treated against locusts, at 700–900 g product/ha (560–720 g carbaryl/ha).

Lucerne may be treated against leaf rollers, leaf hoppers and the lucerne flea, at 350–1.4 kg product/ha (280 g–1.1 kg carbaryl/ha).

For millipede control, the product is diluted to 50 g/5 L (8 g carbaryl/L) to cover 30 m^2 (equivalent to 1.33 g carbaryl/m^2) and sprayed onto garden beds and compost heaps, paths around buildings or around walls to form a 1 m high protective barrier.

The 2004 First Aid Instructions and Safety Directions (FAISD) Handbook (DoHA, 2004b) entry for products containing carbaryl at a concentration greater than 1% specifies First Aid Instructions '**a**'. (If poisoning occurs contact a doctor or poisons information centre.) and '**h**' (If swallowed, give one atropine tablet every 5 minutes until dryness of the mouth occurs; if poisoned by skin absorption or through lungs, remove any contaminated clothing, wash skin thoroughly and give atropine tablets as above. Get to a doctor or hospital quickly.).

The product label bears statement '**a**' but statement '**h**' appears in its previous wording, which instructs the care-giver to induce vomiting, preferably using ipecac syrup. Because all reference to induction of vomiting has been now removed from the FAISD Handbook, the product label should be amended accordingly.

The label complies with the current Safety Directions for carbaryl wettable powder (WP), LD and suspension concentrate (SC) products of all strengths, which are as follows:

Product is poisonous if absorbed by skin contact or swallowed.	120 130 131 133
Avoid contact with eyes and skin.	210 211
Do not inhale (dust) (spray mist).	220 (221 WP) 223
When preparing spray, wear elbow-length PVC gloves.	279 281 290 294
If product on skin, immediately wash area with soap and water.	340 342
After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.	350
After each day's use, wash gloves.	360 361

500 g/kg suspension concentrate

The three products in this category are intended for agricultural, industrial and domestic situations. Nufarm Flowable Carbaryl 500 Insecticide is available in 2.5 and 5 L HDPE containers with opening sizes of 38 mm for the 2.5 L pack, and 38 or 63 mm for the 5 L pack. These pack sizes are also available in tin cans with 44 mm openings. A 20 L drum is marketed in HDPE (with a 58 or 63 mm opening) or steel (with a 63 mm opening). Bugmaster Flowable Insecticide is marketed in 5, 10 and 20 L containers, while the pack sizes for David Grays Carbaryl 500 Flowable Insecticide are 1, 5 and 20 L.

The products are applied by dilute or concentrate spraying. The dilution rates cited below are those specified for dilute spraying. Lower dilution rates may be used for concentrate spraying but these are not specified because they will vary with the equipment used, crop type and growth stage. Users are directed to shake the container before slowly adding the concentrate to the water in the spray tank under agitation. Empty containers are to be triple-rinsed before disposal.

Uses on trees and bushes:

- avocados, applied to young trees and at flowering against leaf beetles at 200 mL product/100 L (1 g carbaryl/L)
- macadamias and pecans, against nutborers, twig-girdlers, leaf beetles and lepidopteran pests at 200 mL product/100 L (1 g carbaryl/L) or 2.2 L product/ha (1.1 kg carbaryl/ha)
- pome and stone fruit for control of insects, mites and slugs during non-fruiting periods, and for pome fruit thinning at 160–200 mL product/L (0.8–1 g carbaryl/L). Bugmaster Flowable Insecticide and David Grays

Carbaryl 500 Flowable Insecticide may also be applied by coarse spray twice during winter to trunks and limbs of stone fruit trees damaged by borers, at 290 mL product/100 L (1.5 g carbaryl/L)

- duboisia, against caterpillars, moths, beetles and locusts at 200 mL product/100 L (1 g carbaryl/L) or 2.2 L product/ha (1.1 kg carbaryl/ha)
- rosella, for treatment of beetles at 200 mL product/100 L (1 g carbaryl/L)
- kenaf, against leaf beetles, at 2.2 L product/ha (1.1 kg carbaryl/ha)
- ornamentals including roses, at 150–200 mL product/100 L (0.75–1 g carbaryl/L) or 1.8–2.2 L product/ha (0.9–1.1 kg carbaryl/ha). Pests controlled include leaf miners, earwigs, lepidopterans, bugs, beetles, cutworms, grasshoppers and scale
- elms, against leaf beetles as a bark band treatment at 40 mL product/L water (20 g carbaryl/L), using a hand pump or hydraulic sprayer to apply a 50 cm stripe about 1.5 m above ground level or on branches. Alternatively, a foliar spray of 20 mL product/10 L water (1 g carbaryl/L) may be applied.

Potatoes may be treated against moths at 200 mL product/100 L (1 g carbaryl/L) or 2.2 L product/ha (1.1 kg carbaryl/ha). Two or three sprays at 3–4-week intervals are usually required.

Raspberries are treated at 200 mL product/100 L (1 g carbaryl/L) for control of grasshoppers, moths and caterpillars.

Cereal crops, maize and sorghum are treated against midges, bugs, army- and cutworms, grasshoppers and locusts at 160–200 mL product/100 L (0.8–1 g carbaryl/L). Alternative treatment rates of 1.2–2.2 L product/ha (0.6–1.1 kg carbaryl/ha) are also nominated. Aerial spraying is nominated as an application method for cereals. A single rate of 2.2 L product/ha (1.1 kg carbaryl/ha) is nominated for rice, which may require re-treatment after a 14-day interval.

Lucerne, pasture and pasture seed crops are treated at between 160 and 200 mL product/100 L (0.8–1 g carbaryl/L) or 500 mL–2.2 L product/ha (equivalent to 250 g/ha–1.1 kg/ha). Pests controlled include locusts, leafrollers, weevils, cut- and budworms, lucerne fleas, caterpillars, leafhoppers and cockchafers.

Cotton may be treated against bollworms at 200 mL product/100 L (1 g carbaryl/L) or 2.2 L product/ha (1.1 kg carbaryl/ha). Repeat treatments at 7–14-day intervals may be required.

Labels for Nufarm Flowable Carbaryl 500 Insecticide and David Grays Carbaryl 500 Flowable Insecticide include uses on stored grain and grain storage infrastructure. Cereal grain is treated against borers at rates of 10 or 16 mL product/te grain (5 or 8 g carbaryl/te). Although no dilution rate is specified, application is by means of standard grain-spraying machinery, which usually applies a diluted spray mixture on the conveyor or auger. Disinfestation of grain storage buildings may be performed using a 10 mL product/L mixture (5 g carbaryl/L), with an application rate of 1 L/10 m^2 (equivalent to 0.5 g carbaryl/m^2). Surfaces are sprayed to runoff.

Label instructions also include a variety of pest control uses. Non-crop, domestic, commercial and industrial areas, and rights of way may be treated. A mixture consisting of 55 mL product/10 L (2.75 g carbaryl/L) may be sprayed liberally on the exterior walls of houses, outbuildings, fences and breeding places for control of earwigs. Some labels nominate knapsack spraying as a method for use in these situations. Grasshoppers and locusts are controlled using up to 1.4 L product/100 L (7 g carbaryl/L), applied by high-volume ground equipment, usually at 220–1100 L/ha (1.5–7.7 kg carbaryl/ha). Ants, moths, fleas and weevils are controlled using a 2.2 L product/100 L spraymix (11 g carbaryl/L). Applicators are instructed to thoroughly spray surfaces, but to not apply by space spray. However, it is unclear whether indoor areas can be treated.

Tobacco and bulk storage facilities and sheds may be treated against crawling arthropods and moths at 200 mL product/10L (10 g carbaryl/L). A 5 L volume of the prepared spray mixture is applied per 100 m^2, equivalent to 0.5 g carbaryl/m^2.

Eradication of insect nests can be undertaken with mixtures containing 130–320 mL product/L (65–160 g carbaryl/L) for wasps and 1.1 L product/100 L (5.5 g carbaryl/L) for bees. The liquid is poured, sprayed or squirted into the nest.

The product label for Nufarm Flowable Carbaryl 500 Insecticide also includes a single veterinary use. Pigs may be treated for lice and mange by spraying them to wetness with a mixture of 50–100 mL product/10 L water (2.5–5 g carbaryl/L). Repeat application after a 10–14-day interval is required.

The First Aid Instructions and Safety Directions appearing on the product labels conform to those recommended in the FAISD Handbook. The label for Bugmaster Flowable Insecticide warns users not to re-enter treated areas until spray deposits have dried, and to wear cotton overalls and elbow-length PVC gloves if prior entry is required.

37 g/kg soap bar

This product is a 350 g aggregated powder block, branded as Joseph Lyddy G-Wizz Insecticidal Dry Shampoo for Horses and Ponies. It is used for control of ectoparasites by daily application to the affected skin areas.

First Aid Instructions '**a**' and '**h**' appear on the product label, as recommended in the FAISD Handbook. No entry exists in the FAISD Handbook covering Safety Directions for this category of product and a new entry is required. The statements that appear on the product label are as follows: 'Avoid contact with the eyes and skin' (210, 211) and 'Do not inhale dust' (220, 221), and 'Wash hands after use' (351).

2 g/L lotion with 20 g/L sulfur and 50 g/L zinc oxide

Joseph Lyddy Y-Itch Animal Insecticide Bactericide is sold in 500 mL bottles and is used to relieve skin irritation and dermatitis caused by ectoparasites on dogs and horses. The oil-based lotion is rubbed onto the affected skin areas twice daily.

The recommended First Aid Instructions for products containing 1% or less carbaryl and liquid aromatic hydrocarbons are **'a'** and **'c'**, respectively. These statements should appear on the product label. At the time of assessment, there was no entry in the FAISD Handbook to cover Joseph Lyddy Y-Itch Animal Insecticide Bactericide, and Safety Directions should therefore be set if this product registration is maintained.

2.3 Toxicological hazards of carbaryl

Acute toxicity

Carbaryl acts by inhibiting ChE enzymes in the blood and central and peripheral nervous systems. In lethal-dose studies, the lowest oral LD_{50} for carbaryl in rats was 246 mg/kg bw (moderate toxicity), and the lowest dermal LD_{50} in rabbits was > 2000 mg/kg bw (low toxicity). In rats, the inhalational median lethal concentration (LC_{50}) was 2500 mg/m^3 (4-hour exposure as an aerosol; low toxicity). The effects of acute carbaryl intoxication were consistent with those seen for other carbamate insecticides, and included salivation, tremors, reduced activity and ataxia. In rats, ChE inhibition reached its maximum between 0.5 and 1 hour following carbaryl administration by gavage. The subsequent time course of ChE inhibition was both dose- and tissue/site-dependent. Recovery of plasma and RBC ChE activity was rapid (within 2 hours post-dosing at 10 mg/kg bw and within 24 hours at 50 mg/kg bw). Brain ChE activity was slower to recover, taking at least 24 hours at and above 10 mg/kg bw. Carbaryl was slightly irritating to rabbit eye but was not a skin irritant in rabbits or a skin sensitiser in guinea pigs by topical application. No acute toxicity studies have been performed with the currently registered Australian products containing carbaryl.

Repeat-dose toxicity

In short-term repeat-dose and subchronic studies by the oral route, ChE inhibition occurred in dogs. In rats and monkeys, the target organs were the kidneys and liver, in which hypertrophy occurred, probably associated with enzyme induction. In repeat-dose dermal studies with carbaryl and two carbaryl-based products, rats displayed RBC ChE inhibition at carbaryl doses of 40–50 mg/kg bw/d and brain ChE inhibition at 50–100 mg/kg bw/d. In a chronic study via the oral route in dogs, dose-related plasma, RBC and brain ChE inhibition was seen, together with some abnormalities in haematological and serum biochemical parameters. Carbaryl caused carcinogenic activity in the chronic rodent studies, inducing tumours of the thyroid, urinary bladder and liver in rats, and kidney, liver and vascular system in mice. However, with the exception of vascular tumours, carcinogenicity occurred only at the highest daily doses administered (which were equivalent to or greater than the acute oral LD_{50}), and in the presence of marked systemic toxicity including behavioural changes, cataracts and anaemia. By contrast, vascular tumours developed in male mice even at the lowest dose of 16 mg/kg bw/d. Carbaryl has not demonstrated genotoxicity *in vivo* and in most *in vitro* test systems, and mechanistic studies suggest that the vascular tumours may arise from cellular injury mediated by a reactive electrophilic metabolite. The strength and weight of evidence suggest that carbaryl is unlikely to pose a carcinogenic hazard to humans if they are exposed occasionally to low doses of the chemical.

When administered repeatedly by gavage, carbaryl disrupts spermatogenesis in rats at doses of 5 mg/kg bw/d and above. It has also caused reduced fertility in some multi-generation reproduction studies in rats,

but only at or above comparatively high dietary doses of about 100 mg/kg bw/d. Although causing foetal toxicity, carbaryl has not caused malformations in reproduction or developmental studies in rats or rabbits. Carbaryl's neurotoxicity has been studied extensively. In adult rats, signs of carbamate poisoning and functional deficits in behaviour were correlated with brain, plasma and RBC ChE inhibition. The NOEL in a 13-week neurotoxicity study was 1 mg/kg bw/d and a maternal NOEL of 1 mg/kg bw/d was established on the basis of these same effects in a developmental neurotoxicity study. However, carbaryl had no neurotoxic effects on rat pups from treated dams, no adverse neuropathology findings were made in repeat-dose studies and carbaryl does not cause delayed neuropathy.

Toxicity to humans

Information summarised from the Office of Chemical Safety's reviews of mammalian toxicology

Limited information is available on carbaryl toxicity in humans. Two case studies of adverse effects in humans following carbaryl ingestion have been reported, in which scientists experienced severe but non-fatal anti-ChE poisoning after deliberately ingesting carbaryl at doses of approximately 2.8 and 5.5 mg/kg bw. Atropinisation relieved but did not eliminate the symptoms. Recovery occurred after 2–4 hours. In studies of carbaryl metabolism, oral doses of up to 1 mg/kg bw have been administered to human subjects without apparent ill effects, but ChE activity appears not to have been assayed.

In an epidemiological study of 765 individuals (12 580 person years) involved in carbaryl production and packaging, of whom 51 had died, the overall death rate and mortality from heart disease and malignancy were below those of the USA and the state in which the plant was located. Cohort mortality from heart disease and cancer did not show any significant trend towards increasing with duration of employment at the factory. There was an excess mortality from brain tumours (3 observed vs 0.9 expected) but the result lay well within the range of chance.

Assessment of published epidemiology studies

MCDUFFIE HH ET AL. (2001). NON-HODGKIN'S LYMPHOMA AND SPECIFIC PESTICIDE EXPOSURES IN MEN: CROSS-CANADA STUDY OF PESTICIDES AND HEALTH. CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 10;1155–1163.

Methods

A population-based case control study was conducted among men residing in six Canadian provinces to test whether there was an association between pesticides and non-Hodgkin lymphoma (NHL). The study population consisted of men aged 19 years and over who had been diagnosed with NHL between September 1991 and December 1994. HIV-positive men were excluded. To balance the number of cases by geographical region, each province was assigned a target number of cases, and ascertainment ceased when the required target was reached. Cases were ascertained from provincial cancer registries except in Quebec, for which hospital ascertainment was used. Diagnosis of 436 of the 517 NHL cases was confirmed from hospital records and pathology reports, and by examination of tumour tissue material by one of the study authors. However, subjects whose pathological material was not available were retained in the study.

The control population consisted of 1506 men aged 19 years and over, selected randomly from provincial health insurance records, telephone listings or electoral rolls. Subject selection was stratified by ± 2 years to ensure comparability with the entire case group within each province. Postal questionnaires were mailed to potential members of the study and control populations.

A pilot study was performed to test study procedures and define pesticide exposure, to distinguish between 'intensive' exposure and 'environmental' exposure (which included bystander and incidental exposure). Non-occupational uses of pesticides in home, garden or hobby situations were included. Few individuals were completely free from exposure. The study authors therefore defined 'intensive' exposure as a cumulative total of 10 h/yr to any combination of pesticides (including algicides). Screening questions in the initial postal questionnaire were used to trigger telephone interviews with persons whose exposure was 'intensive'. The 68 pilot study cases and 103 controls did not participate in the main study. A further group of 27 volunteer farmers participated in a validation study of questionnaires modified in light of the pilot study. This group also permitted access to records of their purchase of pesticides.

Postal questionnaires attempted to control for variables known or suspected to be associated with the development of NHL. These included demographic characteristics, medical history, family history of cancer, smoking habit, job history, occupational exposure to selected substances and accidental pesticide spills, and use of personal protective equipment (PPE). Each subject reporting 'intensive' exposure, and a 15% random sample of the remainder, was mailed a list of chemical and brand names, and was subsequently telephoned. Detailed information on pesticide exposure history was obtained by telephone from 119 NHL cases and 301 controls. This information was also obtained from a further 60 randomly chosen NHL cases and 155 controls who had been exposed for less than 10 h/yr. Information gathered included exposure to specific groups of pesticides (herbicides, fungicides, insecticides and fumigants) and individual active constituents. The number of days/year exposure to individual compounds was also ascertained.

Data (including telephone survey data from the random sample that did not report 'intensive' exposure) were analysed statistically, using a sequence of bivariate and multivariate analyses examining the influence of pesticide exposure, major chemical classes, individual active constituents and the number of days' exposure per year. The influence of putative medical risk factors for NHL was also evaluated. Data were stratified by age group and province. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for the medical risk factors, chemical classes, active constituents and frequency of exposure. Any statistically significant ($p < 0.05$) medical variables were used to adjust for the effects of exposure. There was enough statistical power to detect an OR of 2 when at least 1% of the controls were exposed to a particular class of pesticides or individual active constituent.

Results

Some 517 NHL cases and 1506 control subjects responded to postal questionnaires. The group's mean ages were 57.7 and 55.0 years in the NHL and control cohorts, respectively. About 45% of each group had lived on a farm at any time. A slightly but non-significantly higher proportion of the NHL group were classified as having been 'intensively' exposed to pesticides, compared with the controls (26.7% vs 24.2%; OR 1.22 and 95% CI 0.96–1.55). A family history of cancer in a first-degree relative (OR 1.31; 95% CI 1.05–1.62) and

a personal history of another cancer (OR 2.43; 95% CI 1.71–3.44) were associated with significantly increased risk of NHL.

Of the NHL cohort, 37 had been exposed to carbamate insecticides, of which 25 reported exposure to carbaryl. Sixty and 34 controls reported exposure to carbamates and carbaryl, respectively. In the initial bivariate model, the ORs associated with carbamates and carbaryl were significantly elevated. A slight and non-significant elevation in OR was associated with exposure to carbofuran and methomyl. These results are displayed in Table 5 below.

Table 5: Incidence of exposure to carbamate insecticides among NHL cases and controls

	NHL (N = 517)		CONTROL (N = 1506)			
CHEMICAL	NUMBER EXPOSED	% EXPOSED	NUMBER EXPOSED	% EXPOSED	ODDS RATIO^ (95% CI)	ADJUSTED ODDS RATIO* (95% CI)
Carbamates	37	7.2	60	4.0	**1.95 (1.25–3.05)**	**1.92 (1.22–3.04)**
Carbaryl	25	4.8	34	2.3	**2.05 (1.18–3.55)**	**2.11 (1.21–3.69)**
Carbofuran	9	1.7	18	1.2	1.58 (0.68–3.67)	1.64 (0.70–3.85)
Methomyl	6	1.2	13	0.9	1.86 (0.67–5.17)	1.65 (0.54–5.03)

^ Calculated with strata for age and province of residence

* Adjusted for medical variables that had a statistically significant association with NHL

Bolded values are statistically significant ($p < 0.05$)

Phenoxyherbicides, 2,4-D, mecoprop, dicamba, lindane, Aldrin, DDT, organophosphorus insecticides, malathion, amide fungicides, captan, sulfur and carbon tetrachloride were also significant contributors to the risk of NHL. However, when the results were subjected to multivariate (conditional logistic regression) analyses that included major chemical classes *or* individual pesticides together with the medical co-variates for which $p < 0.05$, carbaryl and carbamate insecticides were no longer found to contribute significantly to the risk of NHL. Dicamba, mecoprop and aldrin were the only chemicals for which a significant contribution was found. Carbaryl and carbamates appear to have been omitted from the analysis of exposure frequency and risk of NHL, and so it is not possible to comment on this aspect of the study.

Comment

Although the study authors claimed that the risk of NHL was significantly increased by exposure to carbamate insecticides and carbaryl, their finding was based on a comparatively modest number of exposed individuals. The paper did not state whether these individuals had been exposed to carbaryl only, or had also been exposed to other pesticides. However, most of the NHL and control populations who reported exposure to insecticides had been exposed to two or more insecticidal active constituents. This leaves open the possibility that the results were confounded by multiple exposures, especially given that exposure to

2–4 different insecticidal active constituents was associated with a significantly increased risk of NHL (OR 1.58; 95% CI 1.17–2.13). Moreover, when the data were analysed in conjunction with medical risk factors for NHL, neither carbamates nor carbaryl were significant risk factors. The study is therefore not considered to have provided strong evidence that carbaryl is a significant risk factor for the development of NHL among product users.

ZHENG T ET AL. (2001). AGRICULTURAL EXPOSURE TO CARBAMATE PESTICIDES AND RISK OF NON-HODGKIN LYMPHOMA. JOURNAL OF OCCUPATIONAL AND ENVIRONMENTAL MEDICINE 43(7);641–649.

Methods

To investigate the relationship between agricultural use of carbamate pesticides and risk of NHL, the authors pooled data from two previous population-based case control studies performed in Nebraska, Iowa and Minnesota during the early 1980s with a third conducted in Kansas (Cantor et al., 1992; Hoar et al., 1986; Zahm et al., 1988). Only data from white males were used. A total of 985 subjects diagnosed with NHL and 2895 control subjects were included in the study. Study pathologists confirmed the diagnosis of NHL by reviewing pathology specimens, and grouped the NHL cases into four histological types (follicular, diffuse, small lymphocytic and other).

Information on pesticide use and on other suspected or established risk factors for NHL (family cancer history and smoking habit) was obtained by standardised interviews conducted with the subjects, or their next of kin if the subjects were dead or incapacitated. Interviews were conducted in person or by telephone. The procedures for obtaining information on pesticide use varied significantly between the three studies. Subjects in Iowa, Minnesota and Nebraska were asked whether they had used or handled specific pesticides; whether the pesticides had been used on crops or animals; years of first and last use; and years of use for specific pesticides. In Kansas, duration and intensity measures were obtained for carbamate insecticides and carbamate herbicides as groups, not individual pesticides. Although specific chemicals could be reported, the duration and frequency of use data from these cohorts were in terms of broad categories but not specific chemicals. Information on frequency of use was not collected from Minnesota subjects. This information was collected in Iowa but was excluded from the pooled analysis to avoid bias, because there was a much higher proportion of proxy respondents among the NHL subjects (55%) than controls (28%) in that state.

Subjects who had never lived or worked on a farm (‘non-farmers’) were used as the non-exposed reference population. Unconditional logistic regression models were used to estimate the association between carbamate pesticide use and risk of NHL, and to control for confounding. ORs and 95% CIs were calculated, with the ORs being adjusted for age at diagnosis, type of respondent (proxy or personal interview), state of residence, first-degree family history of cancer, use of hair dye, consumption of water from private wells and tobacco smoking. These variables were included in the final model. Uses of various other pesticides or chemical classes were also adjusted when assessing the risk of NHL.

Results

A history of cancer among first-degree relatives was 8–21% more common among NHL cases than controls (significant at $p < 0.01$). Eleven carbamate pesticides were reported as having been used by farmers. Relative to men who had never farmed, farmers who ever used carbamate pesticides had a 50% higher risk of NHL. Both carbamate herbicides and insecticides were significantly associated with increased risk (see Table 6). The reviewing toxicologist has highlighted risk factors that the study authors claimed were significant. Readers should note that farmers who 'used' the pesticides did not necessarily apply them themselves). Farmers who never used carbamates, however, showed no increased risk. Although the increased risk of NHL was seen in Minnesota, Kansas and Nebraska, it was not evident in Iowa. ORs calculated from all subjects combined tended to be higher than ORs from subjects who had been interviewed directly, suggesting the possibility of recall bias among proxy respondents.

Table 6: Risk of NHL associated with use of carbamates

	ALL SUBJECTS				DIRECT INTERVIEW			
FACTOR	NHL	CONTROL	OR*	95% CI	NHL	CONTROL	OR*	95% CI
Nonfarmers	243	273	1.0		164	442	1.0	
USE OF CARBAMATE PESTICIDES								
Farmers (no use)	488	1392	1.1	0.9–1.4	316	807	1.0	0.8-1.4
Farmers (used)	107	216	1.5	1.1-2.0	82	169	1.3	0.9-1.8
USE OF CARBAMATE HERBICIDES								
Farmers (no use)	612	1771	1.1	0.9-1.4	388	1015	1.1	0.8-1.4
Farmers (used)	60	108	1.5	1.1-2.3	45	86	1.3	0.8-2.0
USE OF CARBAMATE INSECTICIDES								
Farmers (no use)	518	1503	1.1	0.9-1.4	337	873	1.0	0.8-1.3
Farmers (used)	89	172	1.6	1.2-2.2	67	135	1.4	0.9-2.0

* Adjusted for age, proxy or direct interview, state of residence, first-degree family history of cancer, use of hair dye and private wells, and smoking habit.

Carbaryl, carbofuran, butylate and EPTC were used by a sufficient number of subjects to evaluate individually. After adjusting for potential confounding variables, each of these chemicals showed an increased risk (OR = 1.6 in all cases) of NHL among farmers who had used them. Only the results pertaining to carbaryl will be discussed in this assessment.

According to the study authors, the risk of NHL was elevated in farmers who had personally handled carbaryl (OR = 1.8; 95% CI 1.1–2.8) but not among those who had not personally handled the chemical (OR = 0.8; 95% CI 0.3–2.7). There was an elevated risk among those who first used carbaryl over 20 years before diagnosis (OR = 1.8; 95% CI 0.9–3.7) but not among those who first used the chemical less than 20 years previously (OR = 1.1; 95% CI 0.6–2.0). Risk was also elevated in those who had used carbaryl for 7 years

or more (OR = 1.5; 95% CI 0.8–3.0) compared to those who used the chemical for less than 7 years (OR = 1.1; 95% CI 0.6–2.1). ORs calculated for the direct interview group were generally within ± 0.2 of the equivalent values for all subjects, without any consistent trend, but there were a few exceptions. Among the subjects who were interviewed directly, there appeared to be a greater risk for those who used carbaryl for 5 or more days/year (OR = 3.7; 95% CI 0.5–28) than for those who used the chemical less frequently (OR = 1.9; 95% CI 0.6–5.8). However, these latter associations were based on responses from only two and five NHL cases, respectively, and are probably not meaningful. In the direct interview group, analysis of the different NHL tumour types showed a markedly enhanced risk for small-cell lymphoma (OR = 4.0) but only little or no enhancement for the follicular, diffuse and other types (ORs ranged from 0.6 to 1.2).

The study authors performed a further stage of analysis that evaluated the potential confounding effect of other pesticides. Adjustment for organophosphates, 'natural products', 'inorganics', amides and dinitroanilines were said to have had no significant impact on the relationship between carbaryl use and NHL risk. By contrast, 'trazines' [sic], benzoics, heterocyclics and phenoxyacetic acids did show 'individual impacts' on the relationship. These impacts were not quantified. The study authors presented the results of an analysis that controlled for these four classes of pesticides in addition to the confounding variables that were controlled for in the initial analysis. Compared with the initial analysis, findings were similar but the associations between carbaryl and NHL were weakened, with ORs declining by 0.1–0.4.

The risk of NHL remained higher in farmers who used carbaryl than among those who did not (OR = 1.4; 95% CI 0.9–2.2), and the risk of NHL was elevated in farmers who had personally handled carbaryl (OR = 1.5; 95% CI 0.9–2.6) but not among those who had not personally handled the chemical (OR = 0.7; 95% CI 0.2–2.5). There was an elevated risk among those who first used carbaryl over 20 years before diagnosis (OR = 1.6; 95% CI 0.8–3.4) but not among those who first used the chemical less than 20 years previously (OR = 0.9; 95% CI 0.5–1.8). Risk was only slightly elevated in those who had used carbaryl for 7 years or more (OR = 1.3; 95% CI 0.7–2.7) compared with those who used the chemical for less than 7 years (OR = 1.0; 95% CI 0.5–1.9). ORs calculated for the direct interview group were generally within ± 0.3 of the equivalent values for all subjects, without any consistent trend. However, as before, there were some exceptions. Among the subjects who were interviewed directly, there appeared to be a greater risk for those who used carbaryl for 5 or more days/year (OR = 3.3; 95% CI 0.4–26) than for those who used the chemical less frequently (OR = 1.6; 95% CI 0.5–5.0). Again, these latter associations were based on responses from only two and five NHL cases, respectively, and are not meaningful. In the direct interview group, there remained a markedly enhanced risk for small-cell lymphoma (OR = 3.8) but no enhancement for the follicular, diffuse and other types (ORs ranged from 0.8 to 1.1).

Comment

The available manuscript of this paper contains no indication of which results were statistically significant, an unusual omission that hinders its independent interpretation. Overall, the association between NHL and exposure to carbaryl was not strong in spite of the large cohort sizes, and diminished when exposure to other classes of pesticides was taken into account. If carbaryl had indeed been causing NHL in persons occupationally exposed to the chemical, one would have expected the association to increase in strength when the influence of triazines, benzoics, heterocyclics and phenoxyacetic acids was removed. It is also potentially significant that the study authors did not control for the subjects' previous personal history

of other cancers. This factor is strongly associated with the subsequent development of NHL (McDuffie et al., 2001). The most convincing association demonstrated in this study was with the small lymphocytic NHL subtype, but it was based on only 9 cases out of the 985-strong NHL cohort and is therefore of equivocal biological significance.

2.4 Toxicological endpoints for occupational health and safety risk assessment

Dermal absorption factor

Several *in vitro* and *in vivo* studies have been performed investigating the dermal absorption of carbaryl. These were discussed in detail in the OCS toxicology review. Two studies in rats (Cheng, 1994; Cheng 1995) were used to estimate a dermal absorption factor for exposure and risk assessment of persons using carbaryl products in home garden and home veterinary settings. However, this absorption factor was optimised for a comparatively short (2-hour) exposure period. Operators who apply carbaryl in an agricultural or pest control environment may be exposed for an entire 8-hour workday, and so a different dermal absorption factor is required for exposure and risk assessment of professional use products.

The level of percutaneous absorption in rats varied, depending on the dose and formulation applied. Absorption was approximately twice as extensive from Sevin XLR Plus (a water-based product containing 44% carbaryl) than from Sevin 80S (an 80% WP). The highest levels of absorption from Sevin XLR were 2% over 30 minutes and 25% over 24 hours. Corresponding values with Sevin 80S were 0.7% over 30 minutes and 14% over 24 hours. In both cases, there appears to have been a higher rate of absorption early in the exposure period than during the later part. The reasons for the disparity between the formulations are unknown. Although it would be reasonable to suppose that absorption from a liquid (in the presence of surfactants) would occur more rapidly than from a powder, both products were applied in 1% aqueous carboxymethylcellulose vehicle. In any case, regardless of whether the product is in liquid or powder form, mixers, loaders and applicators are likely to be exposed to carbaryl in the diluted spray mixture, in addition to contacting the concentrate. The OCS will therefore adopt a conservative position and base the dermal absorption factor on the results obtained with Sevin XLR Plus, and assume that approximately half of the carbaryl absorbed (that is, 12.5%) had penetrated through the skin over the first third (that is, 8 hours) of the exposure period. Hence, a dermal absorption factor of 12.5% over an 8-hour workday will be used for exposure and risk assessment purposes.

Inhalation absorption factor

A study (Dorough, 1982) evaluated by the WHO (1994) demonstrated that over a 1-hour exposure period, rats retained 75.4% of a 50 µg dose of ^{14}C-labelled carbaryl inhaled as a vapour. Hence, a 75% inhalation absorption factor will be used for exposure and risk assessment purposes.

NOELs for occupational health and safety assessment

Carbaryl products intended for professional use are most likely to be applied by farmers, spray contractors, horticulturists, operators of grain storage facilities and PCOs. With the exception of PCOs, professional product users and agricultural workers are likely to be exposed on a seasonal basis, as dictated by pest pressure and the growth cycle of plants under production. The most likely route of exposure would be by dermal contact with the undiluted products, spray mixture or treated vegetation. Inhalation of carbaryl in spray aerosols or when handling WP products may also occur. Veterinary administration of carbaryl to pigs, horses and dogs could cause applicators and animal handlers to be exposed, again predominantly via the skin.

Depending on pest activity, PCOs may continually use carbaryl products on up to several days per week. Use of carbaryl around or within residential, commercial and industrial buildings could also result in exposure of building occupants if they make contact with treated surfaces. However, although exposure of building occupants or residents may occur over several successive days until the applied carbaryl degrades, there may be prolonged intervals between applications to any single property. Given its comparatively low vapour pressure (1.2×10^{-6} to 3.1×10^{-7} mm Hg at 24–25^{o}C), building occupants or persons in other situations are unlikely to receive significant exposure to carbaryl vapour.

Dermal and inhalation NOELs must therefore be set for assessment of occupational exposure and exposure of building occupants, using data generated over timescales appropriate to the likely frequency and duration of exposure.

Dermal NOELs for occupational exposure assessment

Agricultural and veterinary uses

Most operators using carbaryl products in agricultural and veterinary settings will be exposed seasonally. In these circumstances, toxicology studies of up to 28 days' duration are considered to be the most suitable for OHS purposes. With carbaryl, the most sensitive toxicological endpoint in acute and short-term studies is ChE inhibition. However, in common with most other carbamates, carbaryl dissociates rapidly from the active site of ChE enzymes. Inhibition occurs over a brief time span, typically over 2 or a few hours, and there is comparatively low scope for successive exposures to cause a cumulative effect. Therefore, short-term operator exposure to carbaryl may be considered as a series of independent, acute (single-dose) exposures.

Under these circumstances, a NOEL for OHS assessment purposes could be based on an acute toxicity study. However, although acute neurotoxicity studies have been performed with carbaryl in rats, ChE inhibition occurred at the lowest dose of 10 mg/kg bw. It is therefore necessary to consider short-term repeat-dose or subchronic studies instead. Four such studies that are adequate for regulatory purposes have been performed with carbaryl: a 25-day developmental neurotoxicity study in rats by gavage administration, a 28-day rat dermal study, a subchronic neurotoxicity study by gavage in rats, and a 5-week dietary study in dogs. In the oral studies, rats were more sensitive than dogs to anti-ChE effects, and so the OHS NOEL should be based on data from rats. Plasma and RBC ChE were of equivalent sensitivity to carbaryl. Therefore, when

considering human exposures over a limited timeframe, RBC ChE activity may be used to set a NOEL for OHS risk assessment of carbaryl, in the absence of data on plasma ChE activity.

Because they remove errors and uncertainty associated with extrapolation between different routes of administration, dermal repeat-dose studies form the optimal basis for setting a dermal NOEL for OHS purposes. In the 28-d rat dermal study with carbaryl (Austin, 2002), only RBC and brain ChE activities were measured. The NOEL for both endpoints was 20 mg/kg bw/d. This value will be used in the current risk assessment relating to exposure from application of carbaryl in agricultural settings and re-entry into treated crops. The acceptable margin of exposure (MOE) is ≥ 100, resulting from application of a 10-fold uncertainty factor for inter-species extrapolation and a 10-fold factor for intra-species variability.

Pest control operator uses

As discussed above, the pattern of PCO exposure to chemicals is expected to vary from exposure in an agricultural situation. In addition to potentially being exposed to a particular chemical for several days per week, PCOs are considered more likely to apply a chemical throughout the year. Therefore, a separate OHS NOEL is required to cover PCOs, and should be based on the most sensitive toxicological endpoints in chronic exposure or other long-term studies. Although a long-term or chronic study via the dermal route would be ideal for this purpose, no such studies with carbaryl are available. The assessment must therefore be performed using studies undertaken by oral administration.

The most toxicologically significant effect of carbaryl following long-term administration is the formation of vascular system tumours, which occurred in male mice during a 2-year study (Hamada, 1993) at the lowest administered dose of 16 mg/kg bw/d. The strength and weight of evidence is that carbaryl does not mediate genotoxicity, and is therefore unlikely to pose a carcinogenic hazard to humans provided that exposure is constrained to sufficiently low levels. Accordingly, the OCS will base the risk assessment for PCO exposures on the LOEL of 16 mg/kg bw/d for tumour formation (adjusted for a dermal absorption of 12.5% to 128 mg/kg bw/d), but with an acceptable MOE of ≥ 2000. The MOE is derived from a 10-fold uncertainty factor for inter-species extrapolation, a 10-fold uncertainty factor for intra-species variability, a 10-fold safety factor for use of a LOEL instead of a NOEL, and a further 2-fold factor allowing for any remaining uncertainty as to the mode and mechanism of tumour formation. No correction for an internal dose is required since carbaryl is almost completely (90%) absorbed from the gastrointestinal tract.

Inhalation NOEL for occupational exposure assessment

Agricultural and veterinary uses

Inhalational exposure to carbaryl in an agricultural setting would most probably arise from inhalation of spray aerosols, or dust generated when handling WPs. The pattern and frequency of exposure would be the same as for dermal exposure. Although a short-term repeat-dose inhalation study would be the preferred basis for establishing an inhalation NOEL, none has been performed with carbaryl. Therefore, the inhalation NOEL must be based on a suitable study by oral administration. The most sensitive short-term toxicological endpoint for carbaryl is plasma, RBC and brain ChE inhibition, for which NOELs of 1 mg/kg bw/d were established in 13-week neurotoxicity and developmental neurotoxicity studies (Robinson & Broxup, 1996,

1997) in rats. Adjusting for the inhalation absorption factor of 75%, the resulting NOEL becomes 1.3 mg/kg bw/d. The acceptable MOE is ≥ 100, resulting from application of a 10-fold uncertainty factor for inter-species extrapolation and a 10-fold factor for intra-species variability.

PCO uses

As discussed above, the more continual pattern of PCO exposure requires the use of long-term studies to derive an inhalation OHS NOEL. Since none have been performed with carbaryl via the inhalation route, an oral study must be used instead. Again, the most suitable basis for assessment of occupational risks is the study of Hamada (1993), in which the LOEL for tumour formation was 16 mg/kg bw/d. Adjusting for the inhalation absorption factor of 75%, the resulting LOEL becomes 21 mg/kg bw/d. The acceptable MOE will be ≥ 2000, derived from a 10-fold uncertainty factor for inter-species extrapolation, a 10-fold uncertainty factor for intra-species variability, a 10-fold safety factor for use of a LOEL instead of a NOEL, and a further twofold factor allowing for any remaining uncertainty as to the mode and mechanism of tumour formation. No correction for an internal dose is required since carbaryl is almost completely (90%) absorbed from the gastrointestinal tract.

NOEL for re-entry interval calculations

Re-entry into treated crops

Persons re-entering treated crops may be exposed to carbaryl residues on vegetation or fruit. Exposure would most probably occur via the skin, and on a seasonal basis. As is the case for pesticide applicators in an agricultural setting, re-entry exposure to carbaryl may be considered as a series of independent single dose exposures, and ChE inhibition is the most relevant toxicological endpoint. Hence, the 28-day dermal study in rats by Austin (2002), in which the NOEL for RBC and brain ChE inhibition was 20 mg/kg bw/d, will be used to derive a NOEL for re-entry exposure and risk assessment. The NOEL does not require adjustment for route-to-route extrapolation or systemic dose. The acceptable MOE is ≥ 100, resulting from application of a 10-fold uncertainty factor for inter-species extrapolation and a 10-fold factor for intra-species variability. Given the low volatility of carbaryl, an inhalation NOEL for persons re-entering treated crops will not be established.

Re-entry into treated premises

The use of carbaryl within and around residential, commercial and industrial buildings and grain storage facilities will cause the occupants to be exposed dermally if they make contact with treated surfaces. No information is available on the persistence of carbaryl indoors or on hard or paved surfaces. However, the half-life of carbaryl dislodgeable foliar residues (DFRs) on outdoor turf is approximately 3 days (Mester, 1999), suggesting that carbaryl may persist in or around buildings for several days post-application. Thus, building occupants are most likely to experience an isolated episode of exposure, or a short series of exposures over a few days.

Vandekar (1965, evaluated by WHO, 1994) found plasma ChE inhibition and elevated urinary excretion of the carbaryl metabolite 1-naphthol in villagers whose homes had been treated a week previously with

carbaryl by surface spray. Hence, the 28-day dermal study in rats by Austin (2002), in which the NOEL for RBC and brain ChE inhibition was 20 mg/kg bw/d, will be used to derive a NOEL for building occupants. The NOEL does not require adjustment for route-to-route extrapolation or systemic dose. The MOE is ≥ 100, resulting from application of a 10-fold uncertainty factor for inter-species extrapolation and a 10-fold factor for intra-species variability. Given the low volatility of carbaryl, an inhalation NOEL for building occupants will not be established.

2.5 Assessment of occupational exposure and risk during application

Evaluation of exposure studies

Studies evaluated in the WHO EHC review of carbaryl

During airblast spraying of orchards, Jegier (1964) found air concentrations in the range of 0.18–0.81 mg/m^3, with a mean of 0.6 mg/m^3. The mean inhalation exposure measured by the respirator pad technique was 0.29 mg/h (range: 0.24–0.53 mg/h). Mean dermal exposure, measured by skin pads, was 25 mg/h (range: 18.5–30.3 mg/h). The maximum total exposure was 31 mg/h. However, it is unclear whether these exposures were experienced by mixer/loaders or applicators, and the dilution and application rates are unknown.

Another study on the exposure of workers operating tractor-drawn airblast equipment (Comer et al, 1975) while applying a 0.045–0.06% carbaryl spray found a mean respiratory exposure of 0.09 mg/h (range: 0.01–1.08 mg/h) and a mean dermal exposure of 59 mg/h (range: 1.70–212 mg/h). Respiratory exposure was estimated from the amount of carbaryl deposited on respirator pads, while dermal exposure was estimated from dermal pads and calculated on the basis of a worker wearing a short-sleeved, open-necked shirt without gloves or a hat.

Studies evaluated by the Office of Chemical Safety

MERRICKS DL (1997a). CARBARYL APPLICATOR EXPOSURE STUDY DURING APPLICATION OF SEVIN 5 DUST TO DOGS BY THE NON-PROFESSIONAL. STUDY NOS: 1517 (LAB) AND 10565 (SPONSOR). LABS: AGRISEARCH INC., FREDERICK, MD, USA; RHONE-POULENC AG COMPANY, RESEARCH TRIANGLE PARK, NC, USA; AND MORSE LABORATORIES INC., SACRAMENTO, CA, USA. SPONSOR: RHONE-POULENC AG COMPANY, RESEARCH TRIANGLE PARK, NC, USA. STUDY DURATION: 17 FEBRUARY TO 22 AUGUST 1997. REPORT DATE: 22 AUGUST 1997.

QA:	Yes.
GLP:	US EPA 40 CFR Part 160 (1989).
Test guideline:	US EPA Subdivision U, Applicator Exposure Monitoring Series 231 and 232, Occupational and Residential Exposure Test Guidelines Group A, Application Exposure Test Guidelines.

Study design

This study assessed carbaryl inhalational and dermal exposure among a group of volunteers, under conditions intended to simulate the use of a home veterinary insecticide in compliance with label directions. The study group consisted of 20 male and non-pregnant female volunteers aged 19–45 years who had given informed consent before participation. The volunteers' mean weight was 78.8 kg and mean height was 1.73 m. None of the study group was professional pet groomers.

The product used was Sevin Carbaryl Insecticide 5 Dust (manufactured by Solaris Group/Aerofil Technology Inc, St Louis, MO, USA, lot 20187A), a 5.38% active constituent powder formulation registered by the US EPA for control of fleas and ticks on dogs and cats. The non-active constituents present in the product were not stated. The product was applied directly from the shaker top dispenser in which it was packaged.

Forty replicate exposures were performed. Twenty exposures were carried out with the applicator wearing household type latex gloves, while the remainder were performed without gloves. Each volunteer conducted one replicate with gloves followed by a replicate without gloves. Throughout the procedure, volunteers wore cotton long-sleeved shirts and long pants over a cotton whole-body dosimeter. Their footwear was covered with lab booties before entry into the application area. Breathing zone monitoring was performed using a personal air-sampling pump operating at 2 L/min with an OVS sorbent tube containing XAD-2 resin.

The exposure phase of the study was undertaken in a heated, cement-floored external garage attached to a dog pound, where the study animals were housed. The dogs used in the study were chosen randomly and were of various breeds, weighing between 1.8 and 57 kg (mean = 21 kg). Each replicate exposure commenced with a volunteer opening a single 0.45 kg can of the product by pushing the seal tab into the can top and opening the multiple shaker holes. The volunteer then dusted three previously untreated dogs with the product, working the powder into the coat of each animal by hand. After completion of the task, the used can of insecticide was handed to the study laboratory staff. To minimise cross-contamination, individual areas were used for exposure and sampling. The floor was rinsed and towelled dry between replicates.

Detergent washes were then performed on the volunteer's hands, face and neck wipes were taken, and shirts, pants and whole-body dosimeters were removed, sectioned, wrapped in aluminium foil and bagged. Samples were placed on dry ice and then stored frozen. Air pumps and tubing were cleaned after each replicate, and OVS sorbent tubes were capped, bagged and stored frozen. Volunteers were subsequently resuited and provided with a new air-sampling tube before performing the second replicate.

To allow compensation for any effects of weathering on carbaryl, wash and wipe samples, OVS tubes and pieces of clothing and inner dosimeters were fortified with known amounts of the test chemical and exposed to the environment for 20 minutes under conditions similar to those during application. Blank control washing, wiping and clothing samples and OVS tubes were treated similarly. Handling and storage procedures were the same as those adopted for the samples from volunteers.

Carbaryl was extracted from facial wipes, dosimeters and external clothing sections with acetone and subjected to Florisil Bond Elut cleanup before analysis by HPLC. The same analytical method was used for

handwash solutions following dichloromethane extraction and Florisil SPE cleanup if required. Carbaryl trapped in OVS sorbent tubes was extracted with acetonitrile for HPLC assay. The limit of quantitation for OVS tubes was 0.01 μg, and for all other samples was 1.0 μg.

Results

Canine dusting caused significant operator exposure. Most volunteers held each dog against their body while applying the dust or otherwise made body contact with the animals, and in some cases caused a cloud of dust to rise into the air as they worked. Some dogs shed hair during treatment and dog hair was observed to adhere to the outer clothing of one volunteer.

The mean time spent applying the product to three dogs was 7 minutes (range = 5–13 minutes), during which a mean total of 65.3 g of dust was applied (equal to 3.5 g carbaryl, range = 0.65–10 g). Within the groups of three animals, the mean amount of carbaryl applied per dog was 1.2 g (range = 0.15–3.3 g/dog). When adjusted for bw, the mean carbaryl dose per kg of three dogs was 57 mg/kg.

The average post-weathering recovery of carbaryl from fortified face and neck wipes was 88%, and sample residue levels were adjusted accordingly. Over 90% recovery of carbaryl was achieved for hand washings, clothing, inner dosimeters and OVS sorbent tubes, and so no adjustments were made to field sample results from these matrices.

The highest residue levels of carbaryl were found on the external clothing, particularly the lower leg (110–37 000 μg), upper leg (257–387 000 μg) and lower arm (924–67 900 μg). There was gross (up to 300-fold) inter-individual variation in the deposition of carbaryl on all parts of the shirt and pants. Total carbaryl residues on outer clothing are shown in Table 7.

Transfer of carbaryl across the outer clothing to the internal dosimeter was not extensive when averaged across the entire body, with a geometric mean value of 4.5% being obtained. However, the lower arm was especially prone to exposure, with a maximum penetration rate of 28% being attained, although penetration exceeded 10% during only 13/40 replicate procedures. Exposures may have occurred under the cuff, which was sometimes observed to ride up the arm while treating dogs. Penetration through the pants was restricted to 0.1–6%.

The data suggested that although there was a tendency for the carbaryl levels on inner dosimeters to correlate positively with those on the outer clothing, the association was not consistent. There were numerous examples where a high deposition rate on the external clothing did not lead to extensive carbaryl residues on the inner dosimeter. Conversely, there were several examples where one or more individual sections of the inner dosimeter were more heavily contaminated than would be expected from carbaryl levels on the external clothing.

When gloves were not worn, there was extensive exposure via the hands, upon which carbaryl levels were 10-fold higher than those accumulating on the internal dosimeter (see Table 7) and accounted for 90% of total dermal residues. However, gloves reduced exposure to approximately 2% of the geometric mean

carbaryl levels deposited on the unprotected hands. Again, there was gross variation in the amount of carbaryl detected, irrespective of whether gloves were worn.

Carbaryl levels found on the face and neck were low, being approximately 10% of those deposited on the inner dosimeter (see Table 7). The highest OVS sorbent tube residue was 71 μg, which would extrapolate to an inhalation exposure of 1027 μg, assuming a 29 L/min breathing volume.

When exposure from all sources (inhalation, hands, face, neck and inner dosimeter = skin under external clothing) was summed, the mean exposure to carbaryl was 1111 μg and 7986 μg, with and without gloves, respectively. When normalised for volunteer bw and the amount of active constituent used, carbaryl exposure was 4.8 and 36 μg/kg bw/g applied, with and without gloves.

Table 7: Exposure to carbaryl by volunteers applying a 5.4% powder to dogs

	UNGLOVED HANDS		GLOVED HANDS	
	MEAN ± SD	RANGE	MEAN ± SD	RANGE
Application time (minutes)	7 ± 2	5.0–13	No separate data	–
Active constituent applied (g)	3.5 ± 1.8	0.65–10	No separate data	–
Total carbaryl residue on inner dosimeter (μg)	765 ± 3.4	63–13 153	No separate data	–
Carbaryl on lower shirt sleeves (μg)	6 727 ± 2.7	924–67 900	No separate data	–
Carbaryl on lower trouser legs (μg)	1 660 ± 5.3	110–37 000	No separate data	–
Total carbaryl residue on outer clothing (μg)	16 213 ± 2.8	1 643–131 190	No separate data	–
Carbaryl on hands (μg) N = 20	6 999 ± 1.6	3 870–24 600	124 ± 3.4	5.0–917
Carbaryl on face/neck (μg)	62 ± 2.6	8.9–320	No separate data	–
Total dermal exposure (μg)* N = 20	7 826	–	951	–
Estimated carbaryl inhalation at 29 L/min breathing vol (μg)	160 ± 2.5	27–1027	No separate data	–
Total exposure (μg)*	7 986	–	1111	–
Total exposure (μg active constituent/kg bw/g active constituent applied)	36	–	4.8	–

^ N=40 replicates except where indicated otherwise. Arithmetic mean ± SD are given for application time and active constituent applied; all other results are expressed as geometric mean ± SD.

* Excludes carbaryl residues deposited on shirt and pants.

Comment

When applying dust to dogs, the mean inhalation exposure was 45.71 mg/kg carbaryl handled and the dermal exposures would have been as follows:

PPE	HEAD	BODY	HANDS	TOTAL (mg CARBARYL/ kg HANDLED)
Nil	17.71	4 632	2 000	6 650
Overalls	17.71	2 19.6	2 000	2 237
Overalls + gloves	17.71	219.6	35.43	272.7

The corresponding value for the top-of-range inhalation exposure was 293.4 mg/kg carbaryl handled, and the dermal exposures would have been:

PPE	HEAD	BODY	HANDS	TOTAL (mg CARBARYL/ kg HANDLED)
Nil	91.43	37 483	7 029	44 603
Overalls	91.43	3 758	7 029	10 878
Overalls + gloves	91.43	3 758	262	4 111

MERRICKS DL (1997b) CARBARYL MIXER/LOADER/APPLICATOR EXPOSURE STUDY DURING APPLICATION OF RP-2 LIQUID (21%), SEVIN READY TO USE INSECT SPRAY OR SEVIN 10 DUST TO HOME GARDEN VEGETABLES. STUDY NOS: 1519 (LAB) AND 10564 (SPONSOR). LABS: AGRISEARCH INC, FREDERICK, MD, USA; RHONE-POULENC AG COMPANY, RESEARCH TRIANGLE PARK, NC, USA; AND MORSE LABORATORIES INC., SACRAMENTO, CA, USA. SPONSOR: RHONE-POULENC AG COMPANY, RESEARCH TRIANGLE PARK, NC, USA. STUDY DURATION: 12 MAY – 15 DECEMBER 1997. REPORT DATE: 15 DECEMBER 1997.

QA: Yes.
GLP: US EPA 40 CFR Part 160 (1989)
Test guideline: US EPA Subdivision U, Applicator Exposure Monitoring Series 231 and 232, Occupational and Residential Exposure Test Guidelines Group A, Application Exposure Test Guidelines.

Study design

This study assessed carbaryl inhalational and dermal exposure among a group of volunteers, under conditions intended to simulate use of three home garden insecticides in compliance with label directions. The sections on the use of the ready-to-use insect spray and dust will be omitted from this assessment. The study group consisted of 70 male and non-pregnant female volunteers aged 19–72 years who had given informed consent before participation. None of the study group was professional spray applicators. The product trialled was Sevin Liquid Brand Carbaryl Insecticide (manufactured by Solaris Group/Aerofil Technology Inc., St Louis, MO, USA, lot 20527/B1237), a 22.4% active constituent liquid formulation.

Exposures were performed according to the study design tabulated below in Table 8.

Table 8: Exposure studies

PRODUCT	APPLICATION EQUIPMENT	GLOVES	REPLICATES
Liquid (22.4%)	Hose-end sprayer	Yes	20
Liquid (22.4%)	Hose-end sprayer	No	20
Liquid (22.4%)	Hand-held pump sprayer	Yes	20
Liquid (22.4%)	Hand-held pump sprayer	No	20

In each replicate, a volunteer loaded (and where necessary, mixed) and applied the product to two 6 m long rows of mature, vegetable-bearing tomatoes and a single 6 m long row of cucumbers, and then cleaned out the spray apparatus. Throughout each procedure, volunteers wore cotton long-sleeved shirts and long pants over a cotton whole body dosimeter. Breathing zone monitoring was performed using a personal air-sampling pump operating at 2 L/min with an OVS sorbent tube containing XAD-2 resin. Air pumps were activated during the loading, mixing and cleanup phases of the procedure, in addition to the application period.

When using a hose-end sprayer, the product was poured directly into the sprayer jar, which was then attached to the sprayer. The sprayer dial was set to 4 tsp [20 mL]/US gal [3.79 L] water and plants were sprayed to runoff at 275 kPa water pressure, delivered via a garden hose. Unused product was returned to the container and the spray equipment was rinsed with the hose.

Hand-held sprayers were filled with 2 US gal [7.6 L] of water, following which 8 tsp [40 mL] of the product was measured out, added, and mixed by agitation with the sprayer top closed. Further spray mix was prepared as necessary until the task was completed.

Following application/cleanup, detergent washes were performed on the volunteers' hands, face and neck wipes were taken, and shirts, pants and whole-body dosimeters were removed, sectioned, wrapped in aluminium foil and bagged. Samples were placed on dry ice and then stored frozen. Air pumps and tubing were cleaned after each replicate, and OVS sorbent tubes were capped, bagged and stored frozen. Volunteers were subsequently resuited and provided with a new air-sampling tube before performing any subsequent replicate.

To minimise cross-contamination, the study area was designed to avoid walking through previously treated areas while conducting later replicates. Temperature, relative humidity, wind speed and wind direction were recorded during each replicate. To allow compensation for any effects of weathering on carbaryl, wash and wipe samples, OVS tubes and pieces of clothing and inner dosimeters were fortified with known amounts of the test chemical and exposed to the environment for 20 minutes under conditions similar to those during application. Blank control washing, wiping and clothing samples and OVS tubes were treated similarly. Handling and storage procedures were the same as those adopted for the samples from volunteers.

Carbaryl was extracted from facial wipes, dosimeters and external clothing sections with acetone and subjected to Florisil Bond Elut cleanup before analysis by HPLC. The same analytical method was used for hand-wash solutions following dichloromethane extraction and Florisil SPE cleanup if required. Carbaryl trapped in OVS sorbent tubes was extracted with acetonitrile for HPLC assay. The limit of quantitation for OVS tubes was 0.01 μg, and for all other samples was 1.0 μg.

Results

Detailed observations were made of the volunteers as they performed the loading, mixing, spraying and cleanup tasks. The procedure took an average of 18–23 minutes and the volunteers applied an average of 7.5 and 23 g carbaryl with the hand-held pump and hose-end sprayers, respectively.

Some volunteers brushed against sprayed foliage, spilled or splashed themselves with spray mix or rinsate, touched their faces or had to resolve problems with the equipment. During the exposure periods, the wind speed ranged from 0–11 km/h, the temperature lay between 20 and 33°C, and humidity was 45–86%.

The average post-weathering recovery of carbaryl from fortified face and neck wipes, clothing and inner dosimeters was approximately 80%, and sample residue levels were adjusted accordingly. Some 91% recovery of carbaryl was achieved for hand washings and 98% for the active constituent in OVS sorbent tubes, and so no adjustments were made to field sample results from these matrices.

Use of the hose-end sprayer resulted in approximately 3 times as much carbaryl being deposited on the external clothing and hands as when hand-held pump sprayers were used. However, the difference is attributable mainly to the larger amount of active constituent expended from the hose-end unit. For both sprayer types, the highest residue levels of carbaryl were found on the external clothing and ungloved hands. Indeed, if gloves were not worn, similar amounts of the active constituent were deposited on the hands as were detected on the total surface area of the shirt and pants (see Table 9). The most heavily contaminated parts of the clothing were the lower and upper pants leg (up to 8121 and 1338 μg, respectively) and lower shirt sleeve (up to 400 μg with hand-held pumps and 3037 μg with hose-end units). There was extensive (70-fold) inter-individual variation in the total deposition of carbaryl on the external clothing and unprotected hands.

Gloves were highly effective at reducing manual contact with carbaryl. Mean carbaryl levels on the protected hand were no more than 0.35% of those detected when gloves were not worn, irrespective of the type of sprayer used (see Table 9).

Transfer of carbaryl across most volunteers' outer clothing was not extensive. The majority of inner dosimeter samples contained no detectable residues. When the mean residue levels on the outer clothing and inner dosimeter are compared, overall penetration was approximately 1.2% with hand-held sprayers and 0.67% with hose-end sprayers. Localised penetration occurred most often across the lower shirtsleeves, but the highest amount of carbaryl detected in a single region was 180 μg, on the front torso of a volunteer who had used a hose-end sprayer. This individual had been observed to create splashback during cleanup. Although there was a tendency for carbaryl levels on inner dosimeters to correlate positively with those on the outer clothing, the association was not consistent. There were instances where a high deposition rate on

the external clothing failed to cause extensive carbaryl residues on the inner dosimeter. Conversely, there were a few examples where the inner dosimeter was more heavily contaminated than would be expected from carbaryl levels on the external clothing.

Carbaryl levels found on the face and neck were low or undetectable, using both sprayer types. Mean levels found on the face and neck were about 10% of those deposited on the inner dosimeter (see Table 9). Very little carbaryl was detected in the breathing zone air and the highest individual OVS tube residue was 0.03 μg, which would extrapolate to an inhalation exposure of only 0.38 μg, assuming a 29 L/min breathing volume.

Mean carbaryl exposure from all sources (inhalation, unprotected hands, face, neck and inner dosimeter = skin under external clothing) was 861 μg and 236 μg, using hose-end and hand-held pump sprayers, respectively. When adjusted for bw and the amount of active constituent used, carbaryl exposure was 0.5 and 0.4 μg/kg bw/g applied, with the respective sprayer types. If gloves were worn, total exposure levels were reduced by factors of approximately 130 and 40, with hose-end and hand pump sprayers, respectively.

Table 9: Exposure to carbaryl by volunteers mixing and applying a 22.4% liquid to vegetables

	HOSE-END SPRAYER		HAND PUMP SPRAYER	
SPRAY APPARATUS	MEAN ± SD	RANGE	MEAN ± SD	RANGE
Application time (minutes)	4 ± 1	2–7	10 ± 3	3–17
Active constituent applied (g)	23 ± 9.5	5.0–49	7.5 ± 1.3	4.6–9.3
Total carbaryl residue on inner dosimeter (μg)	5.3 ± 2.6	3.0–184	4.3 ± 1.9	3.0–30
Total carbaryl residues on outer clothing (μg)	787 ± 3.4	31–8508	345 ± 2.8	69–4876
Carbaryl on hands (μg), **gloves worn** (N = 20)	0.07 ± 3.35	< 1.0–3.9	0.82 ± 2.8	< 1.0–20
Carbaryl on hands (μg), **unprotected** (N = 20)	830 ± 3.1	63–4440	242 ± 2.4	51–2100
Carbaryl on face/neck (μg)	0.61 ± 2.52	< 1.0–58	0.54 ± 1.6	< 1.0–9.8
Total dermal exposure (μg)*, **gloves worn** (N = 20)	6.9	–	5.8	–
Total dermal exposure (μg)*, **hands unprotected** (N = 20)	861	–	236	–
Est. carbaryl inhalation at 29 L/min breathing vol (μg)**	0.09 ± 1.5	0.07–0.25	0.14 ± 2.0	0.07–0.49
Total exposure, **gloves worn** (μg active constituent/ kg bw/g active constituent applied) (N = 20)	0.004	–	0.011	–
Total exposure, **hands unprotected** (μg active constituent/kg bw/g active constituent applied) (N = 20)	0.49	–	0.44	–

^ N=40 except where stated otherwise. Arithmetic mean ± SD are given for application time and active constituent applied; all other results are expressed as geometric mean ± SD.

* Not presented by study author; calculated by multiplying μg exposure/g active constituent by amount of active constituent applied. Excludes carbaryl residues deposited on shirt and pants.

** For calculation purposes, ½ limit of quantitation (0.005 μg) was used when the residue was not detected.

Conclusions

When untrained volunteers applied a 22.4% liquid product to vegetables, the mean exposure to carbaryl was 861 and 236 μg, using hose-end and hand-held pump sprayers, respectively. When adjusted for bw and the amount of active constituent used, carbaryl exposure was 0.5 and 0.4 μg/kg bw/g applied, with the respective sprayer types. If gloves were worn, total exposure rates were reduced to 0.004 and 0.011 μg/kg bw/g applied, with hose-end and hand pump sprayers, respectively.

Comment

When using a hand pump sprayer, the mean inhalation exposure was 0.01867 mg/kg carbaryl handled and the dermal exposures would have been as follows:

PPE	HEAD	BODY	HANDS	TOTAL (mg CARBARYL/ kg HANDLED)
Nil	0.072	46.00	32.30	78.37
Overalls	0.072	0.573	32.30	32.95
Overalls + gloves	0.072	0.573	0.109	0.754

The corresponding value for the top-of-range inhalation exposure was 0.06533 mg/kg carbaryl handled, and the dermal exposures would have been:

PPE	HEAD	BODY	HANDS	TOTAL (mg CARBARYL/ kg HANDLED)
Nil	1.307	650.0	280.0	931.3
Overalls	1.307	4.000	280.0	285.3
Overalls + gloves	1.307	4.000	2.667	7.974

MERRICKS DL (1998) CARBARYL MIXER/LOADER/APPLICATOR EXPOSURE STUDY DURING APPLICATION OF RP-2 LIQUID (21%) TO FRUIT TREES AND ORNAMENTAL PLANTS. STUDY NOS: 1518 (LAB) AND 10564 (SPONSOR). LABS: AGRISEARCH INC., FREDERICK, MD, USA; RHONE-POULENC AG COMPANY, RESEARCH TRIANGLE PARK, NC, USA; AND MORSE LABORATORIES INC., SACRAMENTO, CA, USA. SPONSOR: RHONE-POULENC AG COMPANY, RESEARCH TRIANGLE PARK, NC, USA. STUDY DURATION: 7 APRIL 1997 – 23 JANUARY 1998. REPORT DATE: 23 JANUARY 1998.

QA: Yes.
GLP: US EPA 40 CFR Part 160 (1989).
Test guideline: US EPA Subdivision U, Applicator Exposure Monitoring Series 231 and 232, Occupational and Residential Exposure Test Guidelines Group A, Application Exposure Test Guidelines

Study design

This study assessed carbaryl inhalational and dermal exposure among a group of volunteers, under conditions intended to simulate use of a home garden insecticide in compliance with label directions. The study group consisted of 20 male and non-pregnant female volunteers aged 18–66 years who had given informed consent before participation. The volunteers' mean weight was 80.7 kg and mean height was 1.75 m. None of the study group was a professional spray applicator. The product used was Sevin Liquid Brand Carbaryl Insecticide (manufactured by Solaris Group/Aerofil Technology Inc., St Louis, MO, USA, lot 20527/B1237), a 22.4% active constituent liquid formulation registered by US EPA for use on fruit and nut trees, vegetables, ornamentals, flowers and shrubs.

Forty replicate exposures were performed. Twenty exposures were by hose-end sprayer, while the remainder employed a hand-held pump sprayer. Each volunteer conducted one replicate with each type of equipment. Throughout the procedure, volunteers wore cotton long-sleeved shirts and long pants over a cotton whole-body dosimeter. No hat or gloves were worn. Breathing zone monitoring was performed using a personal air-sampling pump operating at 2 L/min with an OVS sorbent tube containing XAD-2 resin. Pumps were activated during the loading, mixing and cleanup phases of the procedure, in addition to the application period.

The procedure began by opening the product bottle. When using a hose-end sprayer, the product was poured directly into the sprayer jar, which was then attached to the sprayer. The sprayer dial was set to 4 tsp [20 mL]/US gal [3.79 L] water, two citrus trees 2–3 m tall and two ornamental plants 1–1.5 m tall were sprayed to runoff using a 3 US gal/min water flow, delivered via a garden hose. Unused product was returned to the container and the spray equipment was rinsed with the hose.

Detergent washes were then performed on the hands, face and neck wipes were taken, and shirts, pants and whole-body dosimeters were removed, sectioned, wrapped in aluminium foil and bagged. Samples were placed on dry ice and then stored frozen. Air pumps and tubing were cleaned after each replicate, and OVS sorbent tubes were capped, bagged and stored frozen.

Volunteers were subsequently resuited and provided with a new air-sampling tube before performing the pump sprayer replicate. A 2 US gal [7.6 L] volume of water was placed in the sprayer, following which 8 tsp [40 mL] of the product were measured out, added, and mixed by agitation with the sprayer top closed. Further spray mix was prepared as necessary. Two citrus trees and two ornamentals were sprayed as before, residual spray mix was discarded and the spray equipment was rinsed by hose. The volunteers' outer clothing, inner dosimeter, face and hands were then treated as described previously.

To minimise cross-contamination, the study area was designed to avoid walking through previously treated areas while conducting later replicates. Temperature, relative humidity, wind speed and wind direction were recorded during each replicate. To allow compensation for any effects of weathering on carbaryl, wash and wipe samples, OVS tubes and pieces of clothing and inner dosimeters were fortified with known amounts of the test chemical and exposed to the environment for 20 minutes under conditions similar to those during application. Blank control washing, wiping and clothing samples and OVS tubes were treated similarly. Handling and storage procedures were the same as those adopted for the samples from volunteers. A storage stability study was also undertaken over a 32-week period with all sample matrices except OVS tubes.

Carbaryl was extracted from facial wipes, dosimeters and external clothing sections with acetone and subjected to Florisil Bond Elut cleanup before analysis by HPLC. The same analytical method was used for hand wash solutions following dichloromethane extraction and Florisil SPE cleanup if required. Carbaryl trapped in OVS sorbent tubes was extracted with acetonitrile for HPLC assay. The limit of quantitation for OVS tubes was 0.01 μg, and for all other samples was 1.0 μg.

Results

Detailed observations were made of the volunteers as they performed the loading, mixing, spraying and cleanup tasks. The entire procedure took an average of 13 minutes (range 8–18 minutes) when using the hose-end sprayer and 18 minutes (range 12–21 minutes) when using the hand-held sprayer. A number of the volunteers brushed against sprayed foliage or had to resolve problems when loading or cleaning the spray equipment. During the exposure periods, the wind speed ranged from 0–16 km/h, the temperature lay between 14 and 27°C, and humidity was 40–95%.

Application by hose-end sprayer was accomplished in about one-third of the time required to treat the same number of trees by hand-held pump sprayer. However, about twice as much carbaryl was expended when using the hose-end unit than with the hand-held pump sprayer (see Table 10). The mean elapsed time from start to finish of the load–mix–spray–cleanup procedure was 13 minutes (range = 8–18 minutes) with a hose-end sprayer and 18 minutes (range = 13–22 minutes) with a hand-held pump sprayer.

The average post-weathering recovery of carbaryl from fortified face and neck wipes, clothing and inner dosimeters was approximately 80%, and sample residue levels were adjusted accordingly. Approximately 90% recovery of carbaryl was achieved for hand washings and OVS sorbent tubes, and so no adjustments were made to field sample results from these matrices.

For both sprayer types, the highest geometric mean residue levels of carbaryl were found on the external clothing, particularly the leg (168–493 μg) and lower arm (66–100 μg). The lowest residues were present on the rear torso (8.5–20 μg) and upper arm (11–18 μg), followed by the front torso (30–39 μg). There was gross (60- to 900-fold) inter-individual variation in the deposition of carbaryl on the leg and lower arm. The study authors believed that much of the variability was caused by splashes during cleanup, rather than residues deposited when spraying. Total carbaryl residues on outer clothing are shown in Table 10.

Transfer of carbaryl across the outer clothing was not extensive. Most of the inner dosimeter samples contained no detectable residues. The highest penetration rate was 4.5%, from the lower arm to the inner dosimeter. Penetration through the pants was restricted to 0.1–4%, possibly because the pants were made of thicker material than the shirt and had less tendency to become wetted during spraying or cleanup. The data suggested that although there was a tendency for the carbaryl levels on inner dosimeters to correlate positively with those on the outer clothing, the association was not consistent. There were numerous examples where a high deposition rate on the external clothing did not lead to extensive carbaryl residues on the inner dosimeter. Conversely, there were several examples where the inner dosimeter was more heavily contaminated than would be expected from carbaryl levels on the external clothing.

By far the largest source of exposure was the hands, upon which carbaryl levels were similar to those accumulating on the entire external clothing (see Table 10). Residues were slightly higher following use of the hose-end unit than the hand-held pump sprayer. But if the greater active constituent use from the hose-end unit is taken into consideration, this type of apparatus was associated with less carbaryl deposition per g applied. Again, there was gross variation in the amount of carbaryl detected. The highest residue of 13 200 μg was attained following use of the hose-end sprayer, about 20 times greater than the mean from either type of apparatus and over 100-fold greater than the lowest hand residue levels.

Carbaryl levels found on the face and neck were low or undetectable, using both sprayer types. Mean levels found on the face and neck were about 10% of those deposited on the inner dosimeter (see Table 10). Very little carbaryl was detected in the breathing zone air and the highest OVS tube residue was 0.03 μg, which would extrapolate to an inhalation exposure of only 0.38 μg, assuming a 29 L/min breathing volume.

When exposure from all sources (inhalation, hands, face, neck and inner dosimeter = skin under external clothing) was summed, the mean exposure to carbaryl was 743 and 524 μg, when using hose-end and hand-held pump sprayers, respectively. When normalised for bw and the amount of active constituent used, carbaryl exposure was 0.6 and 0.8 μg/kg bw/g applied, with the respective sprayer types.

Table 10: Exposure to carbaryl by volunteers mixing and applying a 22.4% liquid to four trees

	HOSE-END SPRAYER		HAND PUMP SPRAYER	
SPRAY APPARATUS	MEAN ± SD	RANGE	MEAN ± SD	RANGE
Application time (minutes)	4.0 ± 2.0	2.0–7.0	11 ± 2.0	8.0–14
Active constituent applied (g)	17 ± 9.4	9.1–41	8.0 ± 1.0	5.8–9.3
Total carbaryl residue on inner dosimeter (μg)	6.1 ± 2.2	3.0–27	7.6 ± 2.0	3.0–34
Total carbaryl residues on outer clothing (μg)	685 ± 4.0	59–8 629	1074 ± 3.0	28–5 277
Carbaryl on hands (μg)	737 ± 4.0	82–13 200	516 ± 2 .0	139–3 080
Carbaryl on face/neck (μg)	0.6 ± 1.8	< 1.0–3.6	0.7 ±2.4	< 1.0–20
Total dermal exposure (μg)*	743	–	524	–
Estimated carbaryl inhalation at 29 L/min breathing vol (μg)**	0.09 ± 1.51	0.07–0.29	0.12 ± 1.96	0.07–0.38
Total exposure (μg active constituent/kg bw/g active constituent applied)	0.62	–	0.83	–

^ N=20. Arithmetic mean ± SD are given for application time and active constituent applied; all other results are expressed as geometric mean ± SD.

* Excludes carbaryl residues deposited on shirt and pants.

** For calculation purposes, ½ limit of quantitation (0.005 μg) was used when the residue was not detected.

Conclusions

Under simulated home garden conditions involving the application of a 22.4% liquid insecticide product to two large and two small trees, untrained volunteers were exposed to a mean of 743 and 524 μg carbaryl when using hose-end and hand-held spray apparatus, respectively. Greater than 99% of exposure was via the ungloved hands. When normalised for bw and the amount of active constituent used, carbaryl exposure was 0.6 and 0.8 μg/kg bw/g applied, with the respective sprayer types.

Comment

When using a hand pump sprayer to apply carbaryl to trees, the mean inhalation exposure was 0.0150 mg/kg carbaryl handled and the dermal exposures would have been as follows:

PPE	HEAD	BODY	HANDS	TOTAL (MG CARBARYL/ KG HANDLED)
Nil	0.088	134.3	64.50	198.8
Overalls	0.088	0.950	64.50	66.33
Overalls + gloves*	0.088	0.950	0.218	1.256

* Estimated using the mean glove penetration rate from Merricks (1997b)

The corresponding value for the top-of-range inhalation exposure was 0.0475 mg/kg carbaryl handled, and the dermal exposures would have been:

PPE	HEAD	BODY	HANDS	TOTAL (MG CARBARYL/ KG HANDLED)
Nil	2.500	659.6	385.0	1047
Overalls	2.500	4.250	385.0	391.8
Overalls + gloves**	2.500	4.250	3.667	10.42

* Estimated using the top-of-range glove penetration rate from Merricks (1997b)

Estimation of occupational exposure and risk

Estimates of occupational exposure to and of risk from carbaryl have been prepared utilising the results of the exposure studies evaluated under ‘Evaluation of exposure studies’, together with exposure modelling to cover situations for which no experimental data are available. Appropriate adjustments are made for the dilution rates, application rates and use patterns specified by the labels of Australian products. Table 11 lists the assumptions that were applied.

Table 11: Assumptions used in exposure and risk assessment

Bodyweight	70 kg	US EPA (1996)
Body surface area (adult)	1.94 m^2	Derelanko (2000)
Ventilation rate (light activities)	1.0 m^3/h	US EPA (1996)
Normal workday	8 hours with an application period of 6 hours	
Average size of house	Area 170 m^2; volume 430 m^3	
Average industrial building	Area 2500 m^2	
Transmission across gloves	2% (dust or powder)	Merricks (1997a)
Penetration through overalls	5% (dust or powder)	Merricks (1997a)
Protection afforded by half-facepiece respirator with gas/dust cartridges	90%	Thongsinthusak et al. (1993)
Protection afforded by full-facepiece respirator with gas/dust cartridges	98%	Thongsinthusak et al. (1993)
Protection afforded by an enclosed cab	90%	Thongsinthusak et al. (1993)

The situations of use for which exposure and risk estimates have been prepared are:

Scenario (1)	Mixing and loading 800 WP formulation
Scenario (2)	Mixing and loading 500 SC formulations
Scenario (3)	Mixing, loading and application to trees using hand-held equipment
Scenario (4)	Mixing, loading and application to pigs and grain storage using hand-held equipment
Scenario (5)	Application by orchard airblast
Scenario (6)	Application by ground boom sprayer
Scenario (7)	Aerial application: exposure of pilots and flaggers
Scenario (8)	Pest control uses
Scenario (9)	Veterinary administration of 37 g/kg soap bar
Scenario (10)	Veterinary administration of 2 g/L lotion with 20 g/L sulfur & 50 g/L zinc oxide

Scenario (1) Mixing and loading 800 WP formulation

The 800 g/kg WP product is used on tree crops at a dilution rate of 1 g carbaryl/L water. Although no specific method is nominated, application in orchard settings would be by airblast, and mixer/loaders may need to

prepare sufficient spray mix to treat 15 ha/d. Therefore, at an application volume of 1000 L/ha, the mass of carbaryl handled would be 15 kg/d. The product may also be applied to the trunks and limbs of fruit trees at 1.4 g carbaryl/L, a task that would probably be performed with knapsack sprayers or low-pressure handwand equipment used with a vehicle-mounted tank and pump. Operators are unlikely to apply more than 100 or 1000 L of spray mixture by the respective methods, which would require 140 g or 1.4 kg of carbaryl. For use on cereal crops, the 800 g/kg WP is applied at up to 0.72 kg carbaryl/ha, while up to 1.1 kg/ha is applied to lucerne. The product label does not recommend any specific equipment for broadacre spraying but operators are likely to use groundboom equipment, which can achieve a work rate of 50 ha/d. At the highest treatment rate, this would require mixer/loaders to handle 55 kg carbaryl/d. Exposure estimates have therefore been prepared for mixer/loaders handling 0.14, 1.4, 15 and 55 kg of carbaryl in WP form in a single day.

Dermal exposure estimated using the Pesticide Handlers Exposure Database (PHED) No exposure studies covering mixing and loading operations with carbaryl WPs are available. Consequently, the OCS has used PHED model 4, which is for open mixing and loading of WP formulations. The algorithm predicts dermal exposures on the head, body and hands, respectively, of 0.175, 6.885 and 8.010 mg active/kg handled, for a total of 15.07 mg/kg handled. However, the prediction is based on low-quality data and requires corroboration from another source. Assuming 5% and 2% transmission across overalls and gloves (demonstrated experimentally by Merricks, 1997a), 140 g carbaryl could be handled without protective clothing and 1.4 kg could be handled by a mixer/loader wearing overalls. A combination of gloves and overalls would permit a mixer/loader to handle 15 kg carbaryl in WP form. However, the dermal MOE is unacceptable for an operator handling 55 kg of carbaryl when a combination of gloves and overalls is worn (see Table 12). If the mixer/loader wore chemical resistant clothing that conferred a 10-fold further protection factor compared with overalls (that is, a penetration rate of 0.5%), the dermal MOE would remain unacceptable for a person handling 55 kg.

Table 12: Mixing/loading 800 g/kg WP—dermal exposure

		DOSE (MG/KG BW) MOE RELATIVE TO 20 mg/kg BW			
		PRGOTECTIVE CLOTHING			
ACTIVE HANDLED (KG)	EXPOSURE (MG)	NONE	OVERALLS	OVERALLS + GLOVES	CHEMICAL-RESISTANT CLOTHES
0.14	2.11	0.0301 MOE = 666	0.0171 MOE = 1 170	0.00136 MOE > 10 000	0.00074 MOE > 10 000
1.4	21.1	0.301 MOE = 66	0.171 MOE = 117	0.0136 MOE = 1 471	0.00742 MOE = 2 695
15	226	3.229 MOE = 6.2	1.828 MOE = 11	0.146 MOE = 137	0.0795 MOE = 252
55	829	11.84 MOE = 1.7	6.702 MOE = 3.0	0.536 MOE = 37	0.291 MOE = 69

Dermal exposure estimated by the Predictive Operator Exposure Model (POEM) The POEM algorithm for mixer/loaders differs from PHED in that it predicts dermal exposure only on the hands. Rather than deriving estimates with respect to the mass of active handled, POEM assumes that an operator's hands are contaminated with 0.1 g of product each time they open a pack of around 1 kg (no estimate is available for larger packs). When working with an 800 g/kg WP, this would equate to a dermal exposure of 0.08 g carbaryl per opening operation.

In the following table, POEM predictions are shown for operators mixing/loading 55 kg of carbaryl in WP form (sufficient to treat 50 ha) with and without gloves. A 2% transmission rate across gloves is assumed, based on the findings of Merricks (1997a). Since no information on the design of the 800 WP containers is available, estimates have been prepared for 1, 5, 10 and 20 kg packs.

POEM predicts 4400 mg hand contamination when transferring from 1 kg containers. However, it is unlikely that such small packs would be used in broadacre spraying operations.

POEM predicts 880 mg hand contamination where 5 kg packs were used, for which the MOE would be 80 if gloves were worn. The POEM prediction of 480 mg exposure for a mixer/loader opening 10 kg packs is very similar to the PHED prediction of 8.01 X 55 = 441 mg exposure on the hands, but only 58% as extensive as the PHED prediction for whole-body (including hands) dermal exposure (829 mg). This suggests that while PHED's estimate of hand contamination is reasonable, POEM severely underestimates contamination of the body when handling WPs (Table 13).

Although POEM predicts acceptable MOEs if gloves are worn when using 10 and 20 kg packs, the MOEs would be eroded (albeit to an unknown extent) if contamination of the body was taken into account. Hence, PHED remains the preferable model for estimating dermal exposure to carbaryl in WP form.

Table 13: Mixing/loading carbaryl 800 WP-POEM estimate of dermal exposure on hands contamination with 100 mg product or 80 mg carbaryl/opening operation is assumed

CONTAINER	NUMBER OF OPENING OPERATIONS	EXPOSURE (MG CARBARYL)	DOSE (mg/kg BW) MOE RELATIVE TO 20 MG/KG BW	
			PROTECTIVE CLOTHING	
			NONE	GLOVES
1 kg	55	4400	62.9 MOE = 0	1.26 MOE = 16
5 kg	11	880	12.6 MOE = 1.6	0.25 MOE = 80
10 kg	6	480	6.86 MOE = 2.9	0.14 MOE = 146
20 kg	3	240	3.42 MOE = 5.8	0.07 MOE = 292

Inhalation exposure PHED model 4 predicts an exposure rate of 0.098 mg active/kg handled. The prediction is based on medium-quality data and may be used for risk assessment purposes. As shown in the table below, an unprotected mixer/loader can handle 0.14 or 1.4 kg carbaryl in WP form without incurring unacceptable inhalation exposure (Table 14 and Table 15). However, the extent of exposure for an unprotected mixer/loader handling 15 or 55 kg carbaryl is unacceptable. A half-facepiece respirator would be required to maintain the MOE above 100. [Note that POEM does not account for inhalation exposure of mixer/loaders. Therefore, the requirement for respiratory PPE would not have been realised if POEM had been used instead of PHED.]

Table 14: Mixing/loading 800 g/kg WP—inhalation exposure

		DOSE (MG/KG BW) MOE RELATIVE TO 1.3 mg/kg BW		
		RESPIRATORY PROTECTION		
ACTIVE HANDLED (KG)	EXPOSURE (MG)	NONE	HALF-FACE	FULL-FACE
0.14	0.014	0.00020 MOE = 6630	0.00002 MOE > 10 000	0.000004 MOE > 10 000
1.4	0.137	0.00196 MOE = 663	0.00020 MOE = 6630	0.00004 MOE > 10 000
15	1.470	0.021 MOE = 62	0.00210 MOE = 620	0.00042 MOE = 3096
55	5.390	0.07700 MOE = 17	0.00770 MOE = 169	0.00154 MOE = 844

Table 15: Mixing/loading 800 g/kg WP—aggregate exposure

PPE	MOE	MAX. kg FOR MOE ≥ 100
Overalls, gloves, half-facepiece respirator	30	16.5
Overalls, gloves, full-facepiece respirator	35	19.25
Chemical resistant clothes, gloves, full-facepiece respirator	64	35.2

Aggregate exposure The table above shows the aggregate exposure estimated by PHED for a mixer/loader handling 55 kg carbaryl in WP form, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$. Also shown are the maximum quantities of carbaryl that could be handled to maintain the aggregate MOE above 100.

Conclusions Even while wearing chemical-resistant clothing, gloves and a full-facepiece respirator, a mixer/loader could handle a maximum of 35 kg of carbaryl in WP form without incurring unacceptable levels of exposure. This is sufficient for hand-held sprayer use or airblast application to trees, but would treat only

32 ha of lucerne at the highest label application rate, which is 60% of the highest anticipated work rate when using groundboom equipment. Given that it would be impractical to impose a limit on the amount of carbaryl WP that could be handled in a single workday, the use of carbaryl WP products for broadacre application is unsupportable in the absence of data from a suitable exposure study, or adoption of additional measures to reduce exposure of mixer/loaders.

It should be noted that PHED model 5, which is for mixing/loading WPs in water-soluble packaging (WSP), predicts dermal and inhalation exposure rates of 0.088 and 0.00054 mg/kg active handled *without protective clothing or equipment*. These rates are only 0.6% of those predicted for unprotected loader/mixers handling conventionally packaged WPs. Although PHED model 5 is based on low-quality data and can not be used for risk assessment, it does suggest that WSP would confer a highly beneficial reduction in exposure of mixer/loaders. The following table illustrates the MOEs for mixer/loaders preparing 15 or 55 kg carbaryl as WP in WSP. The estimates assume a 95% protection factor relative to conventional WPs (which is probably lower than the true extent of protection), and that no respiratory PPE is worn. An acceptable aggregate MOE can be achieved for a mixer/loader wearing overalls and gloves (Table 16).

Table 16: Margins of exposure for mixing/loading carbaryl as WP in water-soluble packaging

MOE		NO PPE	OVERALLS	OVERALLS AND GLOVES
15 kg	Dermal	124	220	2 740
	Inhalation	1 240	1 240	1 240
	Aggregate	113	186	854
55 kg	Dermal	34	60	740
	Inhalation	340	340	340
	Aggregate	30	52	233
Max. kg for MOE ≥ 100		–	–	128

Hence, if carbaryl 800 g/kg WP products were presented in WSP, exposure of mixer/loaders could be constrained to acceptable levels at significantly higher than anticipated work rates.

Scenario (2) Mixing and loading 500 SC formulations

The 500 g/kg SC products are used on tree and bush crops at a dilution rate of 1 g carbaryl/L water. Although no specific method is nominated, application in orchard settings would probably be by airblast, and mixer/loaders may need to prepare sufficient spray mix to treat 15 ha/d. Therefore, at an application volume of 1000 L/ha, the mass of carbaryl handled would be 15 kg/d. The products may also be applied to ornamental plants at dilution rates of up to 1 g carbaryl/L and to the trunks and limbs of fruit trees at 1.5 g carbaryl/L. These tasks would probably be performed with knapsack sprayers or low-pressure handwand equipment used with a vehicle-mounted tank and pump. Operators are unlikely to apply more than 100 or 1000 L of spray mixture by the respective methods, which would require 150 g or 1.5 kg of carbaryl.

For use on potatoes, cereals, cotton and some tree/bush crops, application rates of up to 1.1 kg/ha are nominated. Broadacre spraying would most probably be by groundboom equipment, which can achieve a work rate of 50 ha/d. At the highest treatment rate, this would require mixer/loaders to handle 55 kg carbaryl/d. During grain disinfestation operations, up to 10 000 tonnes of grain may be treated per day, which would require 80 kg of carbaryl at the highest treatment rate of 8 g/te. Aerial application may cover several hundred ha/d, and so an aerial work rate of 500 ha/d will be used in this assessment. Treatment of 500 ha would require 550 kg carbaryl. Exposure estimates have therefore been prepared for mixer/loaders handling 0.15, 1.5, 15, 55, 80 or 550 kg of carbaryl in SC form.

OPEN MIXING

Dermal exposure No exposure studies covering mixing/loading operations with carbaryl SCs are available. The most suitable method for estimating operator exposure is PHED model 3, which is for open mixing and loading of liquid formulations. The algorithm predicts dermal exposures on the head, body and hands, respectively, of 0.012, 0.677 and 6.390 mg active/kg handled, for a total of 7.079 mg/kg handled. The model is based on high-quality data and can be used for risk assessment. The exposure estimates in the following table utilise the PHED model's default penetration rates of 3.65% and 0.24% across overalls and gloves, respectively (Table 17). It will be assumed that chemical-resistant clothing will provide an additional 10-fold protection factor compared with overalls, and so would allow a 0.4% penetration rate.

Table 17: Open pour mixing/loading 500 g/kg SC—dermal exposure

		DOSE (MG/KG BW) MOE RELATIVE TO 20 mg/kg BW			
		PROTECTIVE CLOTHING			
ACTIVE HANDLED (KG)	EXPOSURE (MG)	NONE	OVERALLS	OVERALLS + GLOVES	CHEMICAL-RESISTANT CLOTHES + GLOVES
0.15	1.03	0.0147 MOE = 1 370	0.0137 MOE = 1 460	0.00011 MOE > 10 000	0.00006 MOE > 10 000
1.5	10.3	0.147 MOE = 137	0.137 MOE = 146	0.00109 MOE > 10 000	0.00063 MOE > 10 000
15	103	1.465 MOE = 13.7	1.370 MOE = 14.6	0.01087 MOE = 1 841	0.00630 MOE = 3 174
55	376	5.370 MOE = 3.8	5.023 MOE = 3.9	0.03984 MOE = 502	0.02311 MOE = 870
80	547	7.811 MOE = 2.6	7.307 MOE = 2.7	0.05795 MOE = 345	0.03361 MOE = 595
550	3760	53.72 MOE < 1	50.24 MOE < 1	0.39841 MOE = 50	0.23107 MOE = 87

In the absence of PPE, the dermal MOEs are acceptable for a mixer/loader handling 0.15 or 1.5 kg carbaryl in SC form. A combination of gloves and overalls is sufficient to assure an adequate MOE for a mixer/loader handling 80 kg carbaryl. However, at the work rate for aerial application, even gloves and chemical-resistant clothing are inadequate to assure an MOE ≥ 100, and engineering controls must be considered as a means of reducing exposure.

CLOSED MIXING

According to PHED model 6, use of a closed liquid mixing/loading system will reduce dermal exposure by a factor of 2.7 relative to open pour methods (based on high-quality data from mixer/loaders wearing overalls and gloves). As illustrated in Table 18, use of closed mixing markedly increases the MOEs, and would enable a mixer/loader to handle 550 kg of carbaryl while wearing overalls and gloves.

Table 18: Closed mixing/loading 500 g/kg SC—dermal exposure

		DOSE (MG/KG BW) MOE RELATIVE TO 20 mg/kg BW			
		PROTECTIVE CLOTHING			
ACTIVE HANDLED (KG)	EXPOSURE (MG)	NONE	OVERALLS	OVERALLS + GLOVES	CHEMICAL-RESISTANT CLOTHES + GLOVES
15	38	0.543 MOE = 37	0.507 MOE = 39	0.00403 MOE = 4 968	0.00234 MOE = 8 570
55	139	1.989 MOE = 10	1.860 MOE = 11	0.01476 MOE = 1 355	0.00856 MOE = 2 349
80	203	2.893 MOE = 7.0	2.706 MOE = 7.3	0.02146 MOE = 932	0.01245 MOE = 1 607
550	1 393	19.90 MOE = 1	18.61 MOE = 1.1	0.14756 MOE = 135	0.08558 MOE = 235

Inhalation exposure PHED model 6 predicts an exposure rate of 0.00019 mg active/kg handled in an enclosed liquid mixing system. The prediction is based on high-quality data and may be used for risk assessment purposes. As shown in Table 19, the extent of exposure for an unprotected operator is acceptable, even at the 550 kg/d work rate.

Table 19: Closed mixing/loading 500 g/kg SC—inhalation exposure

ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (MG/KG BW) MOE RELATIVE TO 1.3 mg/kg BW RESPIRATORY PROTECTION NONE
15	0.003	0.00004 MOE > 10 000
55	0.010	0.00015 MOE = 8 667
80	0.015	0.00022 MOE = 5 909
550	0.105	0.00149 MOE = 872

Aggregate exposure The table below shows the aggregate exposure for a mixer/loader handling 15–550 kg carbaryl SC in a closed system, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$. It can be seen (Table 20) that the MOE for handling 550 kg carbaryl is acceptable and a maximum of 644 kg of carbaryl SC could be mixed using a closed system by an operator wearing gloves and overalls.

Table 20: Closed mixing/loading 500 g/kg SC—aggregate exposure

PPE	ACTIVE APPLIED (KG)	MOE	MAX. kg FOR MOE ≧ 100
Overalls and gloves	15	4 968	644
	55	1 171	
	80	805	
	550	117	

Conclusions Due to the high work rates associated with aerial application, there is potential for toxicologically significant dermal exposure of mixer/loaders unless a closed system is used to prepare carbaryl SC formulations. However, with engineering controls in place, the extent of exposure for a mixer/loader wearing overalls and gloves is acceptable for individuals handling up to approximately 640 kg of carbaryl in SC form. This quantity is sufficient to support aerial application, airblast spraying, groundboom spraying and mechanical spray application to grain at above the highest anticipated work rates. The labels of carbaryl SC products intended for aerial application should be amended to include the relevant engineering controls, and the FAISD Handbook entry for carbaryl SCs should be amended by the addition of Safety Directions to wear overalls and gloves during preparation.

Scenario (3) Mixing, loading and application to trees using hand-held equipment

Carbaryl 800 WP and 500 SC products may be applied to trees and ornamental plants for insect control, either as a foliar spray (at up to 1 g carbaryl/L water) or as a coarse spray onto the trunks or limbs of fruit trees. In the latter case, the dilution rate is 1.4–1.5 g/L. Treatment would probably occur on an *ad hoc* basis, as dictated by pest pressure, and is most likely to involve a few dozen to a few hundred trees or plants in a single workday. Operators would most probably use a knapsack sprayer or a low-pressure handwand in conjunction with a vehicle-mounted tank and pump. The amount of carbaryl used per tree is unknown, but operators are considered unlikely to apply more than 100 L spray mixture in a single workday by knapsack sprayer, or over 1000 L by hand spray from a vehicle-mounted tank. Exposure estimates will therefore be prepared for operators applying 150 and 1500 g carbaryl by the two respective methods. Given the relatively moderate work rate anticipated, it is likely that the same person will prepare and apply the product.

KNAPSACK SPRAYER

Dermal exposure Merricks (1998) measured the exposure of operators who prepared a liquid carbaryl product and applied it to fruit and ornamental trees using hand-held pump sprayers. The highest levels of exposure on the head, body and hands were 2.5, 660 and 385 mg carbaryl/kg applied, for a total of 1047 mg/kg. The worst case penetration rate across a single layer of clothing was 0.64%. Although transmission across gloves was not measured in this study, a worst case rate of 0.95% was observed in a similar study in which carbaryl was applied to vegetables by hand-held pump sprayers (Merricks, 1997b). At these rates of exposure, the dermal MOEs for an operator preparing and applying 150 g carbaryl would be unacceptable, unless gloves and overalls are worn (see Table 21).

Table 21: Mixing, loading and application by knapsack sprayer, SC products—dermal exposure

		DOSE (MG/KG BW) MOE RELATIVE TO 20 mg/kg BW		
		PROTECTIVE CLOTHING		
ACTIVE APPLIED (KG)	EXPOSURE (MG)	NONE	OVERALLS	OVERALLS + GLOVES
0.15	157	2.240 MOE = 8.9	0.840 MOE = 24	0.0223 MOE = 897

Inhalation exposure The highest rate of inhalation exposure in Merricks' (1998) study was 0.0475 mg/kg applied. Therefore, an operator applying 150 g carbaryl by knapsack sprayer would be exposed to up to 0.00712 mg of the chemical, or a dose of 0.00010 mg/kg bw. Relative to the inhalation NOEL of 1.3 mg/kg bw, the MOE is > 10 000. Hence, no respiratory PPE would be required.

Aggregate exposure Given the negligible inhalation exposure, the aggregate MOE would be 897 for an operator wearing overalls and gloves but no respiratory protection. This MOE is highly acceptable, but would apply only where a liquid product was used, given that exposure from mixing/loading a WP is greater than from mixing/loading a liquid. Merricks (1998) did not keep separate records of exposure from the product preparation and application phases of the study. However, the additional exposure from preparing 100 L of spray mixture from a WP can be estimated from Scenario 1. There, dermal and inhalation MOEs of 666 and

6630 were estimated for an unprotected individual mixing/loading 140 g carbaryl in WP form. If the aggregate MOE from preparing the WP (605) is aggregated with the MOE of 897 (from preparing and applying the liquid formulation), then the combined MOE would be 361. This value is acceptable, and in fact underestimates the true MOE.

LOW-PRESSURE HANDWAND, SC PRODUCTS

None of the available exposure studies with carbaryl provide data on application by low-pressure handwand equipment. This assessment will therefore use PHED model 32, which is for open pour mixing and low-pressure handwand application of liquid products.

Dermal exposure PHED model 32 predicts exposures on the head, body and hands of 0.675, 9.72 and 230 mg active/kg applied. Penetration across overalls and gloves is estimated at 2.9% and 0.002%, respectively. Accuracy of the model is limited by the poor quality of the hand exposure data upon which it is based. In particular, the extent of penetration across gloves is anomalously low when compared to the mean (0.34%) and top-of-range (0.95%) values observed by Merricks (1997b) during preparation and application of carbaryl by knapsack sprayer. This assessment will therefore assume 0.95% transmission across gloves rather than the PHED default value. As illustrated in Table 22, the dermal MOE is unacceptable without PPE or with overalls alone, but becomes acceptable if overalls and gloves are worn.

Table 22: Open mixing, low-pressure handwand application, SC products—dermal exposure

ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (MG/KG BW) MOE RELATIVE TO 20 mg/kg BW		
		PROTECTIVE CLOTHING		
		NONE	OVERALLS	OVERALLS + GLOVES
1.5	361	5.151 MOE = 3.9	4.949 MOE = 4.0	0.0673 MOE = 297

Inhalation exposure PHED model 32 predicts an inhalation exposure of 0.0675 mg active/kg applied. The prediction is based on medium-quality data and may be used for risk assessment. A mixer/loader/applicator handling 1.5 kg of carbaryl in SC form would therefore be exposed to 0.101 mg of the chemical, and the dose and MOE would be 0.00145 mg/kg bw and 899, respectively. The MOE is highly acceptable.

Aggregate exposure The aggregate MOE, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$, is 223 for an operator handling 1.5 kg of carbaryl. Up to 3.3 kg of carbaryl in SC form could be mixed in an open system and applied by an operator wearing overalls and gloves. A higher (but unknown) daily work rate could be achieved if mixing and loading were performed in an enclosed system.

LOW-PRESSURE HANDWAND, WP PRODUCTS

In the absence of a relevant exposure study with carbaryl, this assessment will use PHED model 33 for open pour mixing and low-pressure handwand application of WP products.

Dermal exposure PHED model 33 predicts exposures on the head and body of 3.49 and 286 mg active/kg applied. Transmission across overalls is estimated at 3.8%. This value will be used in the risk assessment, given its similarity to the value demonstrated experimentally by Merricks (1997a). Accuracy of the PHED model is limited by the absence of data on exposure of the unprotected hands. However, the model does contain medium-quality data on hand exposure under gloves, which is predicted to be 5.13 mg active/kg applied. Exposure of the unprotected hands will be estimated by back-calculation, assuming a 2% transmission rate across gloves, based on data from Merricks (1997a). Table 23 shows dermal MOEs associated with preparing and applying 1.5 kg carbaryl in WP form. Overalls and gloves are inadequate for limiting exposure to acceptable levels. Even with a combination of chemical resistant clothing and gloves, the MOE fails to attain 100.

Table 23: Open mixing, low-pressure handwand application, WP products—dermal exposure

		DOSE (MG/KG BW) MOE RELATIVE TO 20 mg/kg BW			
		PROTECTIVE CLOTHING			
ACTIVE APPLIED (KG)	EXPOSURE (MG)	NONE	OVERALLS	OVERALLS + GLOVES	CHEMICAL-RESISTANT CLOTHES + GLOVES
1.5	820	11.70 MOE = 1.7	5.808 MOE = 3.4	0.406 MOE = 49	0.208 MOE = 96

Inhalation exposure PHED model 33 estimates inhalation exposure of 2.48 mg active/kg applied based on medium-quality data, and may be used for risk assessment. As demonstrated in Table 24, a half-facepiece respirator would be required to achieve an MOE above 100.

Table 24: Open mixing, low-pressure handwand application, WP products—inhalation exposure

		DOSE (mg/kg BW) MOE RELATIVE TO 1.3 mg/kg BW		
		RESPIRATORY PROTECTION		
ACTIVE HANDLED (KG)	EXPOSURE (MG)	NONE	HALF-FACE	FULL-FACE
1.5	3.720	0.0531 MOE = 24	0.00531 MOE = 240	0.00106 MOE = 1 223

Aggregate exposure Table 25 shows aggregate MOEs, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$, for operators wearing chemical resistant clothing and gloves together with a full- or half-facepiece respirator. It is evident that although the MOE associated with use of a full-facepiece respirator is significantly higher than with a half-facepiece device, an acceptable level is not achieved. Even with the most extensive PPE, a maximum of 1.3 kg of carbaryl in WP form could be prepared by open pour methods and applied by low-pressure handwand before the MOE decreased to an unacceptable level.

Table 25: Open mixing, low-pressure handwand application, WP products—aggregate exposure

PPE	ACTIVE APPLIED (kg)	MOE	MAX. kg FOR MOE ≥ 100
Chemical resistant clothes, gloves & half-face respirator	1.5	69	1.0
Chemical resistant clothes, gloves & full-face respirator	1.5	89	1.3

Conclusions Primarily because of the low amount of carbaryl that would need to be handled during a single workday, exposure of operators preparing and applying SC products to trees and ornamental plants by knapsack spray and low-pressure handwand equipment can be constrained to acceptable levels by gloves and overalls at and above the anticipated work rate. The OCS has no objections to continuation of these uses.

However, exposure modelling predicts that a significantly higher amount of exposure will occur if a WP product was used to treat trees and ornamental plants by low-pressure handwand. At the anticipated daily work rate, there would be scope for toxicologically unacceptable exposure even if the operator wore chemical resistant clothing, gloves and a full-facepiece respirator. Although up to about 1.3 kg of carbaryl in WP form could be applied without eroding the MOE below an acceptable level, it is impractical to impose such a limit on users. While acknowledging the limitations in the exposure model used, the OCS concludes that open mixing and manual application of carbaryl WP products should be discontinued unless mixing/loading exposure is eliminated by providing WSP. Once the product is in WSP, mixer/loader exposure will be similar to that by the SC low hand-held applications, applicator exposure for the required quantity of the active will be acceptable as MOE will be more than 100.

Scenario (4) Mixing, loading and application to pigs and grain storage using hand-held equipment

Nufarm Flowable Carbaryl 500 Insecticide, a 500 g/L SC product, may be used on pigs for treatment of lice and mange by spraying them to wetness with a mixture of 2.5–5 g carbaryl/L water. On the assumption that 100 mL of spraymix (or 0.5 g carbaryl) is applied to each animal and that 1000 animals are treated in a day, the total volume of spraymix would be 100 L and the mass of carbaryl handled would be 0.5 kg. Application equipment would most probably comprise a knapsack or hand-held pump sprayer.

If the operator was exposed to carbaryl at the same rate as predicted in Scenario 3 for use of knapsack spray equipment (see Table 21, page 64), the dermal dose for a person wearing overalls and gloves would be (0.5 ÷ 0.15) X 0.0223 = 0.0743 mg/kg bw. The dermal MOE would therefore be 269. The inhalation dose and MOE for an unprotected operator would be (0.0475 X 0.5) ÷ 70 = 0.000334 mg/kg bw and 3800, respectively. Both these values and the aggregate MOE of 251 are acceptable, and there are no objections to continuation of this use provided overalls and gloves were worn.

Registered uses of 500 g/L SC products also include disinfestation of grain storage buildings, which is performed with a 5 g carbaryl/L spray mixture. Knapsack or low-pressure handwand sprayers would be used. An operator using a knapsack sprayer is unlikely to apply more than 100 L of spray mixture in a day and

would not handle more than 0.5 kg carbaryl. As shown in the preceding paragraph, the aggregate MOE would be 251 for a worker wearing gloves and overalls but no respiratory protection. As outlined under Scenario 3 (page 65), up to 3.3 kg of carbaryl in SC form could be mixed in an open system and applied with low-pressure handwand equipment by an operator wearing gloves and overalls. This is sufficient to treat a 6600 m^2 area. Use of enclosed mixing/transfer systems would enable an even higher work rate.

Conclusions Use of carbaryl 500 g/L SC formulations to treat pigs and disinfest grain storage infrastructure is supported.

Scenario (5) Application by orchard airblast

Both 800 g/kg WP and 500 g/L SC products may be applied to tree crops at a dilution rate of 1 g carbaryl/L or an application rate of 1.1 kg/ha. In either case, approximately 15 kg of carbaryl would be applied at the maximum anticipated work rate of 15 ha/d.

Dermal exposure In the absence of relevant exposure studies, applicator exposure will be estimated using PHED model 11 (airblast, open cab), which predicts exposures of the head, body and hands to be 0.443, 4.185 and 0.276 mg active/kg handled respectively, for a total of 4.904 mg/kg handled. The model is based on high-quality data and may be used for risk assessment. Predicted penetrations across overalls and gloves are 2.26% and 1.98%, respectively. As shown in Table 26, the dermal MOE is acceptable if the applicator wears overalls.

Table 26: Airblast application, open cab—dermal exposure

		DOSE (mg/kg BW) MOE RELATIVE TO 20 MG/KG BW			
		PROTECTIVE CLOTHING			
ACTIVE APPLIED (KG)	EXPOSURE (MG)	NONE	OVERALLS	OVERALLS + GLOVES	CHEMICAL-RESISTANT CLOTHES + GLOVES
15	74	1.050 MOE = 19	0.170 MOE = 118	0.114 MOE = 176	0.098 MOE = 204

Inhalation exposure PHED model 11 predicts an inhalation exposure of 0.01013 mg active/kg handled. Since the prediction is based on high-quality data, it may be used for risk assessment. As shown in Table 27, the anticipated extent of inhalation exposure is acceptable in the absence of PPE.

Table 27: Airblast application, open cab—inhalation exposure

ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (mg/kg BW) MOE RELATIVE TO 1.3 MG/KG BW		
		RESPIRATORY PROTECTION		
		NONE	HALF-FACE	FULL-FACE
15	0.152	0.00213 MOE = 612	0.00021 MOE = 6 120	0.00005 MOE > 10 000

Aggregate exposure Aggregate MOEs, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$, are shown in Table 28 for applicators wearing overalls, or gloves and overalls, without respiratory protection. Also shown is the greatest mass of carbaryl that could be applied while maintaining an MOE ≥ 100. For an applicator wearing overalls, the MOE of 99 lies at the threshold of acceptability. However, there would be no allowance for additional exposure: if the applicator also prepared the spray mixture, the MOE would be eroded below 99 and become clearly unacceptable.

Table 28: Airblast application, open cab—aggregate exposure

PPE	MOE	MAX. kg FOR MOE ≥ 100
Overalls	99	14.9
Overalls and gloves	137	20.6

As shown in the above table, a more adequate MOE can be achieved with PPE comprising overalls and gloves. Under these conditions, if an applicator also prepared the spray mixture from a 500 g/L SC product in a closed system while wearing overalls and gloves, the MOE would be 133. (This is calculated by the equation $MOE_{(M/L/A)} = 1 \div [1/\text{Aggregate } MOE_{(Mixer/Loader)} + 1/\text{Aggregate } MOE_{(Applicator)}]$.) Similarly, the MOE would be 118 if an applicator also prepared the spray mixture from an 800 g/L WP product packaged in WSP, while wearing overalls and gloves. Thus, combined mixing/loading and application operations can be supported.

Conclusion A combination of gloves and overalls provides sufficient protection for persons applying carbaryl by airblast at the anticipated work rate of 15 ha/d. The FAISD Handbook entry for carbaryl SC products has previously been amended by addition of Safety Directions to wear overalls and gloves during application.

Scenario (6) Application by ground boom sprayer

Both 800 g/kg WP and 500 g/L SC products may be applied a rate of 1.1 kg/ha to a variety of broadacre crops that would be amenable to treatment by ground boom equipment. Some 55 kg of carbaryl would be applied at the maximum anticipated work rate of 50 ha/d.

Dermal exposure In the absence of relevant exposure studies, applicator exposure will be estimated using PHED model 13 (ground boom, open cab), which predicts exposures of the head, body and hands to be 0.00362, 0.0857 and 0.0146 mg active/kg handled respectively, for a total of 0.104 mg/kg handled. Given

that the prediction is based on high-quality data, it may be used for risk assessment purposes. As shown in Table 29, the dermal MOE is acceptable even in the absence of protective clothing.

Table 29: Ground boom application, open cab—dermal exposure

ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (mg/kg BW) MOE RELATIVE TO 20 mg/kg BW
		PROTECTIVE CLOTHING
		NONE
55	5.717	0.08168 MOE = 245

Inhalation exposure Based on high-quality data, PHED model 13 predicts an inhalation exposure of 0.00167 mg active/kg handled. As shown in Table 30, the anticipated extent of inhalation exposure is acceptable in the absence of PPE.

Table 30: Ground boom application, open cab—inhalation exposure

ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (mg/kg BW) MOE RELATIVE TO 1.3 mg/kg BW
		RESPIRATORY PROTECTION
		NONE
55	0.0919	0.00131 MOE = 991

Aggregate exposure Table 31 displays the aggregate MOE for an applicator applying 55 kg carbaryl by ground boom, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$. Also shown is the greatest mass of carbaryl that could be applied while maintaining an acceptable MOE. The aggregate MOE is acceptable, and the maximum amount of carbaryl that could be applied is almost double the mass required for the anticipated daily work rate.

Table 31: Ground boom application, open cab—aggregate exposure

PPE	MOE	MAX. kg FOR MOE ≥ 100
Nil	196	108

If an applicator also prepared the spray mixture from a 500 g/L SC product in a closed system while wearing overalls and gloves, the MOE would be 168. (This is calculated by the equation $MOE_{(M/L/A)} = 1 \div [1/\text{Aggregate } MOE_{(Mixer/Loader)} + 1/\text{Aggregate } MOE_{(Applicator)}]$). Similarly, the MOE would be 106 if an applicator also prepared the spray mixture from an 800 g/L WP product packaged in WSP, while wearing overalls and gloves. Thus, combined mixing/loading and application operations could be supported.

Conclusion When applying carbaryl by open cab ground boom spray apparatus, PPE would not be required, based on the comparatively low rate of exposure anticipated.

Scenario (7) Aerial application: exposure of pilots and flaggers

As discussed under Scenario 2, a work rate of 500 ha/d is considered appropriate for aerial spraying operations, which would involve application of 550 kg carbaryl. Mixer/loaders (already covered in Scenario 2), pilots and flaggers may be exposed during aerial spraying. Given that no relevant studies have been submitted, PHED model 7 will be used to estimate exposure of pilots.

PILOTS

Dermal exposure PHED model 7 predicts that the pilot of a fixed wing aircraft with an enclosed cockpit would be exposed respectively on the head, body and hands to 0.00035, 0.00392 and 0.00700 mg active/kg handled, for a total of 0.0113 mg/kg applied. The prediction is based on a sufficient number of high- or medium-quality replicates and is considered adequate for risk assessment purposes. Therefore, in the absence of protective clothing, a pilot applying 550 kg of carbaryl would be exposed to 6.215 mg, or a dermal dose of 0.0888 mg/kg bw. The resulting MOE is 225, a value which is acceptable. Dermal PPE is not required.

Inhalation exposure PHED model 7 predicts that a pilot's inhalation exposure will be 0.00015 mg/kg applied. The prediction is based on medium-quality data and is adequate for risk assessment purposes. Therefore, at the anticipated work rate, inhalation exposure and dose would be 0.0825 and 0.00118 mg/kg bw, respectively. The inhalation MOE of 1103 is acceptable, and so there is no requirement for respiratory PPE.

Aggregate exposure The aggregate MOE for a pilot applying 550 kg carbaryl, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$, is 188. This value is acceptable and indicates that a pilot could apply up to 1032 kg of carbaryl without the need for PPE.

FLAGGERS

During aerial spraying operations, flaggers will be exposed dermally and by inhalation to the active constituent in the spray mixture. This could arise through spray-drift or being overflown while spray is still being released. In addition to the mass of active constituent applied per day, the extent of exposure would also depend on the number of overflights, climatic conditions including wind speed and direction, the concentration of active constituent in the spray mixture and the size of the spray droplets.

PHED model 25 predicts that flaggers will experience a total dermal exposure of 0.119 mg active/kg applied and an inhalation exposure of 0.00079 mg/kg applied. At the anticipated work rate, the inhalation exposure, dose and MOE would be 0.435 mg, 0.00621 mg/kg bw and 209, respectively. The predicted dermal exposure, dose and MOE are 65.4 mg, 0.934 mg/kg bw and 21. These latter values suggest that flaggers should wear dermal PPE to reduce dermal exposure to an acceptable level. However, the PHED algorithm

uses low-quality data for predicting hand exposure under gloves. Moreover, PHED does not take into account the above-mentioned variables that would affect exposure. Consequently, although suggesting the potential for unacceptable dermal exposure of flaggers, PHED model 25 is considered to be an inadequate basis for recommendations on PPE.

Therefore, engineering controls should be considered as a means of limiting exposure of flaggers. According to Thongsinthusak et al. (1993), an enclosed cab will reduce exposure to pesticides by a default value of 90%. If a 90% protection factor is applied to the PHED exposure estimates for flaggers, the dermal and inhalation MOEs would rise by an order of magnitude to 210 and 2090, respectively. The resulting aggregate MOE would be approximately 191, a value that is sufficiently high to allow for any uncertainty arising from the limitations of the available predictive exposure models.

Conclusions Based on exposure modelling, it is unlikely that pilots will be exposed to toxicologically significant quantities of carbaryl during aerial application. By contrast, exposure modelling suggests that flaggers could be exposed via the dermal route to an unacceptable extent, but does not provide sufficiently robust predictions upon which recommendations for PPE can be based. Therefore, when undertaking aerial spraying operations with carbaryl, flaggers should be protected by an enclosed cab unless this measure is proven unnecessary by suitable exposure data gathered under field conditions.

Scenario (8) Pest control uses

Registered uses of carbaryl products include a number of activities which would usually be performed by PCOs. The 800 g/kg WP and 500 SC products may be applied onto the outside walls of buildings or onto the ground to form a protective barrier at concentrations of up to 8 g carbaryl/L water. Domestic, commercial and industrial areas are treated against ants, moths, fleas and weevils with spray mixtures containing up to 11 g carbaryl/L. Applicators are instructed to thoroughly spray surfaces, but to not apply by space spray. Some labels nominate knapsack spraying for use in these situations. The 500 SC product may also be used for treating tobacco and bulk storage facilities and sheds against crawling arthropods and moths at 10 g carbaryl/L. A 5 L volume of the prepared spray mixture is applied per 100 m^2, equivalent to 0.5 g carbaryl/m^2.

KNAPSACK SPRAYER

Knapsack spraying is most likely to be employed to treat domestic premises, or for small tasks in commercial or industrial situations. An average house would probably require about 5 L of spray mixture, containing up to 40–50 g carbaryl. If six houses were treated, the highest number anticipated in a single day, a total of about 250 g of carbaryl would be applied.

Dermal exposure Merricks (1997b) measured the exposure of operators who prepared a liquid carbaryl product and applied it to vegetables using hand-held pump sprayers. The spray was discharged at waist or chest height onto tomatoes, and downwards onto cucumbers. This pattern is similar to that which would occur during spraying of chemical barriers onto walls and the ground or floor. The study is therefore considered relevant to exposure of PCOs applying carbaryl. The highest detected levels of exposure on the head, body and hands were 1.3, 650 and 280 mg carbaryl/kg applied, for a total of 931 mg/kg applied. Based on the top-of-range exposure data, the transmission rates across gloves and a single layer of clothing were

0.95% and 0.62%, respectively. At these rates of exposure, the dermal MOEs for an operator preparing and applying 250 g carbaryl would be unacceptable, unless gloves and overalls were worn (see Table 32). [Note that for PCOs, who may be exposed to carbaryl repeatedly throughout the year, the acceptable dermal MOE is 2000.]

Table 32: PCO uses, knapsack sprayer application—dermal exposure

ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (mg/kg BW) MOE RELATIVE TO 128 mg/kg BW		
		PROTECTIVE CLOTHING		
		NONE	OVERALLS	OVERALLS + GLOVES
0.25	233	3.326 MOE = 38	1.019 MOE = 126	0.0286 MOE = 4480

Inhalation exposure The highest rate of inhalation exposure in Merricks' (1997b) study was 0.0653 mg/kg applied. Therefore, an operator preparing applying 250 g carbaryl by knapsack sprayer would be exposed to up to 0.0163 mg of the chemical, or a dose of 0.00023 mg/kg bw. Relative to the PCO inhalation NOEL of 21 mg/kg bw, the MOE is 91 304. Hence, no respiratory PPE would be required.

Aggregate exposure As calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$, the aggregate MOE for an operator wearing overalls and gloves is 4270, which is acceptable but would apply only where a liquid product was used.

The additional exposure from preparing 250 g of carbaryl in WP form can be estimated from PHED model 4 (as modified in Scenario 1). The dermal exposure for a mixer/loader wearing overalls and gloves would amount to 0.170 mg, or a dermal dose of 0.00243 mg/kg bw. In the absence of respiratory protection, there would be 0.0245 mg exposure by inhalation, or a dose of 0.00035 mg/kg bw. The respective MOEs would be 52 675 and 60 088, and the aggregate MOE would be 28 069. If the aggregate MOE from preparing the WP (28 069) is aggregated with the MOE of 4270 (from preparing and applying the liquid formulation), then the combined MOE would be 3706. This value is acceptable, and in fact slightly underestimates the true MOE.

LOW-PRESSURE HANDWAND, SC PRODUCTS

Larger tasks involving commercial and industrial premises, including storage facilities, are most likely to be performed using a low-pressure handwand in conjunction with a vehicle-mounted tank and pump. A PCO treating two buildings of 5000 m^2 total area at the typical nominated rate of 0.5 g carbaryl/m^2 would mix and apply 2.5 kg of the chemical. Since only the 500 g/L SC products include these uses on their labels, the exposure assessment will not cover carbaryl WPs.

Dermal exposure As discussed under Scenario 3, the most relevant available method for predicting exposure is PHED model 32, which is for open pour mixing and low-pressure handwand application of liquid products. It predicts exposures on the head, body and hands of 0.675, 9.72 and 230 mg active/kg applied. Penetration across overalls is estimated at 2.9%, and it is assumed that chemical resistant clothing will afford

an additional 10-fold protection factor. Due to the poor quality of the hand exposure data upon which the model is based, this exposure assessment will assume 0.95% transmission across gloves (from Merricks, 1997b) rather than the PHED default value.

As shown in Table 33, dermal MOEs for an operator mixing and applying 2.5 kg of carbaryl in SC form are unacceptable, even with PPE comprising gloves and chemical resistant clothing. [Note that for PCOs, who may be exposed to carbaryl repeatedly throughout the year, the acceptable dermal MOE is 2000.]

Table 33: PCO uses, open mixing, low-pressure handwand application, SC products—dermal exposure

		DOSE (mg/kg BW) MOE RELATIVE TO 128 mg/kg BW			
		PROTECTIVE CLOTHING			
ACTIVE APPLIED (KG)	EXPOSURE (MG)	NONE	OVERALLS	OVERALLS + GLOVES	CHEMICAL-RESISTANT CLOTHES + GLOVES
2.5	601	8.661 MOE = 15	7.874 MOE = 16	0.112 MOE = 1140	0.103 MOE = 1241

Inhalation exposure PHED model 32 predicts an inhalation exposure of 0.0675 mg active/kg applied. The prediction is based on medium-quality data and may be used for risk assessment. A mixer/loader/applicator handling 2.5 kg of carbaryl in SC form would therefore be exposed to 0.169 mg of the chemical, and the dose and MOE would be 0.00236 mg/kg bw and 8898, respectively. The MOE is acceptable.

Aggregate exposure The aggregate MOE, calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$, is 1089 for an operator handling 2.5 kg of carbaryl. A maximum of only 1.4 kg of carbaryl in SC form could be mixed in an open system and applied by an operator wearing chemical resistant clothing and gloves.

Effect of enclosed mixing/loading systems The OCS has examined whether the adoption of enclosed mixing systems would confer significant additional protection to PCOs. PHED (model 3) predicts that an unprotected person mixing/loading liquid formulations using open pour methods would be exposed dermally to 7.07 mg active/kg handled. The corresponding value for an unprotected applicator using a low-pressure handwand sprayer (PHED model 18) is 55.1 mg/kg. This implies that when a low-pressure handwand is used, about 10% of a mixer/loader/applicator's total dermal exposure occurs during mixing and loading, while the remaining 90% occurs during application. Therefore, even if exposure during loading/mixing were reduced to zero, or if mixing/loading and application were performed by different operators, the dermal MOE for a PCO operator handling 2.5 kg of carbaryl in SC form would rise from 1241 to only 1380. Exposure would therefore remain unacceptably high.

TREATMENT OF INSECT NESTS

The 500 SC formulations can be used for eradication of insect nests with mixtures containing 130–320 mL product/L (65–160 g carbaryl/L) for wasps and 1.1 L product/100 L (5.5 g carbaryl/L) for bees. The liquid is

poured, sprayed or squirted into the nest, and operators are likely to use a hand-held sprayer fitted with a crack and crevice tool. Such activities would be performed outdoors, and PCOs would seldom be required to destroy more than five nests on a single day. This would consume about 5 L of spray mixture. Exposure estimates will therefore be prepared for an operator handling 5 L spray mixture at the highest recommended concentration of carbaryl (160 g/L).

Dermal exposure In the absence of a suitable exposure study, PHED model 37 (for open pour mixing/loading and application of termiticides) will be used. Based on high-quality data, exposure on the head and body are predicted to be 0.0698 and 30.15 mg active/kg applied. Penetration across a single layer of clothing is estimated at 1.7%. Hand contamination under gloves is predicted at 0.232 mg active/kg applied. Exposure on unprotected hands will be estimated assuming 0.95% transmission across gloves (from Merricks, 1997b). Dermal exposure estimates for a PCO using 800 g carbaryl in SC form for nest eradication are displayed in Table 34. Although MOEs without protection or with overalls alone are < 2000, a combination of overalls and gloves is sufficient to constrain exposure to an acceptable level.

Table 34: PCO uses, mixing and application of 500 SC to insect nests - dermal exposure

ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (MG/KG BW) MOE RELATIVE TO 128 mg/kg BW		
		PROTECTIVE CLOTHING		
		NONE	OVERALLS	OVERALLS + GLOVES
0.80	43.7	0.624 MOE = 205	0.286 MOE = 448	0.00907 MOE = 14 111

Inhalation exposure PHED model 37 predicts an inhalation exposure of 0.00495 mg active/kg applied. The prediction is based on high-quality data and may be used for risk assessment. A mixer/loader/applicator handling 0.8 kg of carbaryl in SC form would therefore be exposed to 0.00388 mg of the chemical, and the dose and MOE would be 0.00006 mg/kg bw and > 200 000, respectively. The MOE is highly acceptable, and given the negligible extent of inhalation exposure, aggregate exposure need not be calculated.

Conclusions Due to their more continuous pattern of exposure, PCOs must be protected from the potentially carcinogenic effects of carbaryl by use of data from a chronic exposure study in conjunction with an enhanced MOE, which has been set at 2000 rather than the usual value of 100. PCOs are expected to handle significantly less carbaryl than operators engaged in agricultural activities. However, even if wearing chemical resistant clothing and gloves, the extent of PCOs' dermal exposure is expected to reach toxicologically unacceptable levels when applying more than about 1.3 kg of carbaryl with hand-held spray equipment. This is less than the mass of carbaryl that could be used for pest control purposes in a single day. Given that it is unfeasible to impose a limit on the amount of carbaryl that could be handled daily, carbaryl should no longer be used for pest control in domestic, commercial and industrial situations, with the exception of insect nest eradication.

Scenario (9) Veterinary administration of 37 g/kg soap bar

Joseph Lyddy G-Wizz Insecticidal Dry Shampoo for Horses and Ponies is a formulated as a 350 g bar or aggregated powder block. The product is used for controlling lice, ticks and mites and leg mange in horses and ponies. Label instructions recommend applying the product on the affected skin areas by drawing it with and against the lay of the coat, which distributes the insecticidal powder. It is to be applied once a day, with repeat applications if necessary. The product would probably be used on an *ad hoc* basis to treat one or a few animals.

When applying the product, users will be exposed to carbaryl by dermal contact, particularly on the hands and arms. Inhalation exposure is also likely, given that powder is normally released from the block and that application would occur within the operator's breathing zone. There are no exposure studies with carbaryl in aggregated powder blocks. However, exposure can be estimated from the study of Merricks (1997a), in which the extent of dermal and inhalation exposure was measured in operators applying a 5.4% carbaryl dust to dogs.

Dermal exposure In Merricks (1997a), dermal exposures were 17.71, 4632 and 2000 mg carbaryl/kg applied, present on the head, body and hands, respectively. Under overalls, exposure on the body decreased to 219.6 mg/kg applied. Use of gloves decreased exposure on the hands to 35.43 mg/kg applied. The mean exposure values will be utilised rather than top-of-range data, given that the release of dust from the block is likely to be more controlled than from the shaker dispensers used by the operators in Merricks' study (Table 35).

Table 35: Use of 37 g/kg bar—dermal exposure

NUMBER OF BARS APPLIED	ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (MG/KG BW) MOE RELATIVE TO 20 mg/kg BW		
			PROTECTIVE CLOTHING		
			NONE	OVERALLS	OVERALLS + GLOVES
1	0.013	86.446	1.23495 MOE = 16	0.41550 MOE = 48	0.05065 MOE = 395

The exposure estimates in the table above are based on an operator applying an entire 350 g block containing 13 g carbaryl, the highest anticipated daily work rate. Unacceptable MOEs have been highlighted. Overalls and gloves would have to be worn to maintain the dermal MOE above 100.

Inhalation exposure In Merricks (1997a), inhalation exposure was 45.71 mg carbaryl/kg applied. As shown in the Table 36, the anticipated extent of inhalation exposure is acceptable in the absence of PPE.

Table 36: Use of 37 g/kg bar—inhalation exposure

NUMBER OF BARS APPLIED	ACTIVE APPLIED (KG)	EXPOSURE (MG)	DOSE (mg/kg BW) MOE RELATIVE TO 1.3 MG/KG BW
			RESPIRATORY PROTECTION
			NONE
1	0.013	0.5942	0.00849 MOE = 153

Aggregate exposure As calculated from the equation $1 \div [1/MOE_{(Dermal)} + 1/MOE_{(Inhalation)}]$, the aggregate MOE is 110, which is acceptable.

Conclusion The continued use of carbaryl as a 37 g/kg dry soap bar for topical veterinary treatment is supported, provided operators wear overalls and gloves when applying the product.

Scenario (10) Veterinary administration of 2 g/L lotion with 20 g/L sulfur & 50 g/L zinc oxide

Joseph Lyddy Y-Itch Animal Insecticide Bactericide is a lotion used to relieve skin irritation and dermatitis caused by a range of ectoparasites, mange and lice in dogs and horses. It is to be applied on the affected skin areas (if possible after clipping the hair around affected areas) after cleaning thoroughly with shampoo and water. The applied lotion should be allowed to dry. Repeat treatment, in the morning and night, is recommended for 3 days, and then every 7 days for 6 weeks.

By extrapolation from the toxicological characteristics of the individual constituents, the product is expected to show low to very low acute oral, dermal and inhalational toxicity, and slight skin and eye irritancy. Given that sulfur and two of the non-active constituents are dermal sensitisers in humans, the product is expected to be a potential dermal sensitiser.

The product contains a non-active constituent that is a reproductive and developmental toxin in rats. However, there is not expected to be a high user exposure to this chemical, given its very low concentration in the product and low rate of dermal absorption.

A second non-active constituent, a liquid hydrocarbon which forms the majority of the product by weight, is a gastrointestinal tract irritant if swallowed, is a slight eye irritant, and may cause respiratory tract irritation, headache, dizziness and nausea consequent to the inhalation of vapours or mists in poorly ventilated areas or at elevated temperatures. The Material Safety Data Sheet recommends the use of eye protection where splashing is expected, and that any routine contact with the material should require use of gloves made of neoprene, nitrile or butyl rubber.

There is no exposure model for this particular product and it is unknown how much would be applied. The amount handled per day could vary markedly depending on the size and number of animals requiring treatment, and the extent of their dermatological disease. As the product is applied manually and massaged into the fur coat, dermal exposure to carbaryl and the non-active constituents will occur, particularly on the

hands and forearms. Aerosols would not be formed during use but there may be inhalation exposure to vapour from the liquid hydrocarbon non-active constituent. However, the extent of inhalation exposure and risk of respiratory tract or central nervous system effects would probably be low because the product is most likely to be used outdoors.

Under these circumstances, it is reasonable to set hazard-based Safety Directions, rather than basing recommendations for PPE on an assessment of operator exposure and risk. Given the use pattern of the product and its anticipated hazards (slight skin and eye irritation, respiratory tract irritation and dermal sensitisation), elbow-length neoprene, nitrile or butyl rubber gloves should be worn during use. Appropriate sensitisation and irritation Warning Statements should appear on the product label.

Risk management of exposure during application

Risk management of carbaryl is complicated by its toxicological characteristics, which create different hazards over different timescales of exposure. In a single exposure or short-term series of exposures, the most sensitive endpoint is ChE inhibition. This pattern of exposure is most relevant to the use of carbaryl products in an agricultural setting. By contrast, in long-term studies in experimental animals, carbaryl has caused the formation of tumours. Therefore, if exposure is prolonged, carbaryl may pose a carcinogenic hazard to humans, even though it probably does not act by causing mutations or other forms of direct damage to genetic material. Consequently, PCOs (who may use carbaryl products continually) must be protected against carcinogenicity, which has been accomplished by basing the risk assessment on a chronic toxicity study and a highly conservative MOE. The OCS has also evaluated epidemiology studies on farmers in Canada and the United States of America, and concluded that there is unlikely to be any causal association between carbaryl use and the subsequent development of NHL, as claimed by their authors.

The foregoing assessment suggests that persons preparing spray mixtures from carbaryl-based WP and SC products are at risk of unacceptable exposure. Based on exposure modelling, it appears that even if gloves and chemical-resistant clothing were worn, mixer/loaders can handle daily no more than about 35 kg of carbaryl in WP form, or 450 kg of carbaryl in SC formulations without eroding the MOE below the acceptable value of 100. These amounts of carbaryl are insufficient to support the anticipated work rates associated with broadacre use of carbaryl. However, exposure can be reduced to acceptable levels with suitable engineering controls, such as enclosed mixing/transfer systems for SC products (this is only relevant for aerial spraying as quantities are used > 450 kg) and use of WSP for WP formulation.

Operators applying carbaryl are likely to be exposed via the dermal route, with the possibility of additional exposure by inhalation. It is not possible to assure the safety of flaggers engaged in aerial spraying operations, unless they are housed within an enclosed cab. However, even at the maximum anticipated daily work rates, spray operators applying carbaryl with airblast or groundboom equipment are less heavily exposed, and engineering controls are not required to protect them. It is also unlikely that pilots will be exposed to toxicologically significant doses of carbaryl during aerial application. Exposure of operators preparing and applying SC products to trees and ornamental plants, grain storage infrastructure and pigs by hand-held spray equipment can be constrained to acceptable levels by gloves and overalls. The OCS has no objections to continuation of these uses. By contrast, exposure modelling predicts that if a WP product was used to treat trees and ornamentals by low-pressure handwand, unacceptable exposure could occur even if

the operator wore chemical-resistant clothing, gloves and a full-facepiece respirator (with open mixing/loading). This use of carbaryl WP products should be discontinued unless WP product can be packed in WSP in 250 g or 500 g and 1 kg pack to eliminate mixer/loader exposures.

Due to the higher MOE necessary to assure the safety of PCOs, predictions based on exposure modelling indicate that even if wearing chemical resistant clothing and gloves, the extent of PCOs' dermal exposure is expected to reach unacceptable levels when applying more than about 1.3 kg of carbaryl with hand-held spray equipment. This is less than the mass of carbaryl that could be used for pest control purposes in a single day. Consequently, carbaryl should no longer be used for pest control in domestic, commercial and industrial situations, with the exception of insect nest eradication. There are no objections to the continuing veterinary use of carbaryl in aggregated powder blocks or lotions, and appropriate Safety Directions have been recommended to support these products.

2.6 Assessment of post-application exposure

Evaluation of surface residue and exposure studies

MESTER TC (1999). CARBARYL: DETERMINATION OF TRANSFERABLE RESIDUES FROM TURF TREATED WITH DRAGON SEVIN LIQUID. STUDY NO.: 98S15602. LAB: ABC LABORATORIES CALIFORNIA, CA, USA. SPONSOR: AVENTIS CROPSCIENCE, RESEARCH TRIANGLE PARK, NC, USA. STUDY DURATION: 21 SEPTEMBER 1998 – 19 JULY 1999. UNPUBLISHED. REPORT DATE: 2 NOVEMBER 1999. AMENDED 4 NOVEMBER 1999.

Test compound: Dragon Sevin Liquid, a liquid containing 25.97% carbaryl technical
Batch: 1209701
GLP & QA: Yes
Guidelines: None

Methods

The study's objective was to determine the levels of carbaryl residues that could be transferred from turf. The study was performed at three field locations in California (CAL), Georgia (GA) and Pennsylvania (PENN). The three sites were treated in October 1998, November 1998 and May 1999, respectively.

The test formulation was Dragon Sevin Liquid, with a nominal carbaryl content of 21.3% (actual content 25.97%). Storage temperature records were kept at the field locations and samples of the product were analysed post-application to verify stability.

The product was applied twice to a 123–240 m^2 turf plot at each location with a 7-day interval between applications. Commercial ground spray equipment or 'equipment simulating commercial ground equipment' was employed. The spray apparatus used at all three sites was equipped with flat fan nozzles spaced 47.5–50 cm apart. Each application was at the maximum nominal label rate of 8.17 lb/acre (0.92 g/m^2, or 92 $\mu g/cm^2$) for a total of 16.34 lb/acre (1.84 g/m^2 or 184 $\mu g/cm^2$). The product was applied in 30–60 gallons water/acre (281–562 L/ha), which was the minimum dilution rate required for thorough coverage of the turf

and thatch layer. A non-treated control plot of 57–94 m^2 area was included at each location, separated by at least 20 m from the treated plots. Following each carbaryl application, test and control plots were irrigated by sprinkler later in the same day. The turf was subsequently watered as required. The plots were mowed as necessary to maintain the desired turf height. The conditions at each test site are summarised in Table 37.

Table 37: Carbaryl transferable residue study: site characteristics and conditions over trial

PARAMETER	CAL	GA	PENN
Grass type	Tall fescue, ~63 mm height, thick thatch	Bermuda grass, prostrate growth with stolons	Tall fescue, 25–31 mm height, very little thatch
Irrigation and precipitation (combined total, mm)	79 in control plot 80 in treated plot	40	68 in control plot 63 in treated plot
Air temperature range (^oC)	1–30	3–32	4–32
Mowing	Before 2nd application and before day 14 sampling	None	Before 2nd application and before day 10 sampling
Application of other chemicals	Fusilade DX applied after day 10 sampling to control bermuda grass infestation	None	None

Turf was sampled from the CAL and GA sites before the 1st application of carbaryl, after the 1st application, after the 1st irrigation, before the 2nd application, after the 2nd application, and 0, 0.5, 1, 2, 3, 5, 7, 10 and 14 days after the 2nd irrigation. Sampling was undertaken once the applied spray or irrigation water had dried, and the study authors did not specify the number of hours between application, irrigation and sampling. The '0.5 day' samples were collected during the evening. The same sampling protocol was followed at the PENN site, except that sampling was performed 0, 0.5, 1, 4, 5, 7, 10 and 14 days after the 2nd irrigation.

At each sampling interval, a sample was collected from each control plot and three replicate samples were collected from each treated plot. The areas to be sampled were chosen randomly. Cotton cloth dosimeters measuring approximately 69 cm X 99 cm were exposed to the turf using the modified California roller method. Dosimeters were attached to sampling frames enclosing an area of 5690 cm^2, placed in contact with the turf, and a 14.5 kg roller was passed forwards and backwards five times over the dosimeters. The cloth dosimeters were cleared of adhering debris, sealed within a metal can and frozen before being transported by freezer truck to the laboratory.

Dosimeters were then stored frozen for between 2 and 5 months until methanol/water extraction and analysis of carbaryl residues by HPLC. The LOD of carbaryl under the study conditions was 0.02 μg/mL, and the LOQ was 2 μg/dosimeter (0.0004 μg/cm^2). Method performance dosimeters treated with 2–10 000 μg carbaryl were extracted and analysed concurrently with the field dosimeters. To control for stability during storage and transport, 'field spike' dosimeters were applied to control turf and then treated with 0, 10 or 500 μg carbaryl.

Post-irrigation residue data from 0 to 14 days after the 2nd application were transformed to natural logarithms and subjected to regression analysis to estimate a decline curve for transferable carbaryl residues at individual locations and for pooled data.

Results

The mean concentration of carbaryl in field samples of Dragon Sevin Liquid was 26.09% following 57–111 days of storage at the field locations. Hence, the product was stable under the study conditions. Achieved application rates were within ± 3% of the target rates.

Recovery of carbaryl from the method controls ranged from 89 to 121% (mean = 104%, SD = 7.7%). Results from field dosimeters were not corrected for analytical recovery. Recovery of carbaryl from 'field spike' dosimeters averaged 102% across the three locations.

During several samplings, moisture was present on the turf, sometimes resulting in wet spots appearing on the dosimeters. The affected samplings were at CAL, 0.5, 3 and 7 days after the 2nd application; GA, 0.5 days after the 2nd application; and PENN, before the 1st application, following the 1st irrigation, and at 0.5, 1, 4 and 5 days after the 2nd irrigation.

Three of 14 untreated control samples from the CAL site contained carbaryl residues at below the LOQ. Carbaryl was not detected in the remaining control dosimeters from CAL. However, carbaryl was detected at concentrations between 0.0004 and 0.0007 $\mu g/cm^2$ on a total of 4 untreated control dosimeters from GA and PENN. The origin of contamination was not identified. Carbaryl was either not detected or not present in quantifiable amounts on the remaining control dosimeters from these locations. The presence of carbaryl on some control dosimeters suggests that spraydrift occurred onto the untreated plots, or there was cross-contamination between dosimeters during sampling or analytical operations. Given that the highest residue level detected on control dosimeters was approximately 2% of the lowest levels present on test dosimeters, these findings are considered insufficient to invalidate the study.

The results from treated sites are summarised in Table 38. Carbaryl transferable residue levels averaged approximately 1 $\mu g/cm^2$ when measured shortly after the 1st and 2nd applications, but before the treated plots were irrigated. The highest value of 1.55 $\mu g/cm^2$ was observed at the CAL site. Following the 2nd application, transferable residue levels at the GA and PENN sites were about 90% and 30% higher, respectively, than levels detected after the 1st application. By contrast, transferable residues at the CAL site were 40% lower after the 2nd application compared with levels following the 1st application. Consequently, there was little increase in pre-irrigation transferable residues if the data from all three sites are combined.

Irrigation of treated turf reduced transferable residue levels by between 20% and 90%, with an average decline of approximately 60% compared to pre-irrigation levels. However, post-irrigation residue levels were about 40% higher following the 2nd application than after the 1st application. The overall average post-irrigation residue level shortly after the 2nd application was 0.497 $\mu g/cm^2$, approximately half the value observed before irrigation.

The subsequent time course of transferable residue levels is illustrated in Table 38. At all three sites, transferable residues measured in the 'day 0.5' samples increased to approximately 1 μg/cm^2, which was up to 3-fold higher than those detected several hours earlier following irrigation. The rise was most marked at the CAL and GA sites. The study author attributed the increase to evening dew formation on the sampled turf, which was considered to facilitate transfer to dosimeters. Despite some between-site variation, transferable residues had decreased to 0.23–0.30 μg/cm^2 by day 3 or 4. By day 14, transferable residue levels had declined to approximately 0.03 μg/cm^2 at all locations.

Table 38: Carbaryl transferable residue study: mean residue levels (μg/cm^2) on dosimeters

TIME	APPLICATION	CAL	GA	PENN	COMBINED SITES
Pre-irrigation	1	1.55	0.696	0.776	1.01
Post-irrigation	1	0.154	0.245	0.439	0.279
Pre-irrigation	2	0.927	1.34	0.997	1.09
Post-irrigation	2	0.290	0.412	0.790	0.497
0.5 day post-irrigation	2	1.08	0.950	0.987	NC
1 day post-irrigation	2	0.303	0.431	0.763	NC
2 day post-irrigation	2	0.240	0.234	ND	NC
3 or 4 day post-irrigation	2	0.227	0.302	0.287	NC
7 day post-irrigation	2	0.041	0.183	0.205	NC
14 day post-irrigation	2	0.035	0.032	0.033	NC

ND = no data

NC = not calculated

The slopes of the transformed residue vs time plots were very similar, being –0.225, –0.218, –0.247 and –0.227 for CAL, GA, PENN and combined data, respectively. The half-life of carbaryl transferable residues was estimated to be 3 days at each location.

Conclusions

Following application to turf at a rate of approximately 0.92 g/m^2 (92 μg/cm^2), transferable residue levels of carbaryl were approximately 1 μg/cm^2, with a highest observed individual value of 1.55 μg/cm^2. The half-life of transferable carbaryl residue on treated turf was approximately 3 days.

Calculation of re-entry intervals

Workers re-entering treated crops, orchards or other areas may be exposed to carbaryl, principally via the dermal route. The most probable source of exposure will be from making contact with carbaryl residues on foliage or fruit. In Table 39, REIs have been calculated for the food and non-food crops for which the continuing use of carbaryl has been confirmed. The calculations assume that:

The initial DFR level will be 2.2 µg/cm^2, which is 1/5th of the usual application rate of carbaryl (1.1 kg/ha). However, where carbaryl may be applied repeatedly at short intervals, a further calculation is performed to cover workers re-entering after the final treatment.

Given that no other residue studies have been submitted, the half-life of carbaryl DFRs will be 3 days, based on the findings of Mester (1999).

Gradient = log2 – log1 ÷ 3 = 0.1

Carbaryl DFR level = $10^{[\log 2.20] + [-0.1 \times \Delta T]}$ where ΔT is the number of days post-application and 0.1 is the gradient of the logDFR level vs time plot.

Dermal dose = (DFR level X TC X 8) ÷ bw where TC is the transfer coefficient and the workday is 8 hours.

Table 39: Re-entry intervals for crops treated with carbaryl

CROP	TC	ACTIVITY	DOSE DAY 0 (mg/kg BW)	MOE DAY 0	REI (DAYS)
Avocados, pome fruit and stone fruit	1000*	Irrigation and scouting	0.251	80	1
Macadamias, pecans (single application)	1000*	Irrigation and scouting	0.251	80	1
Macadamias (4 applications at 2-week intervals)	1000*	Irrigation and scouting	0.251	80	1
Cereal crops, rice, cotton (single treatment)	1000^	Irrigation, scouting, weeding	0.251	80	1
Cotton (2 treatments at a 7-day interval)	1000^	Irrigation, scouting, weeding	0.302	66	2
Potatoes	1000^	Irrigation, scouting, weeding	0.251	80	1
Raspberries	5000~	Harvesting, leaf pulling, thinning, pruning	1.257	16	8
Ornamentals	5000#	Bundling, sorting, cutting	1.257	16	8

* US EPA value for nut trees, high-exposure activities

^ US EPA default associated with low potential for post-application dermal transfer

~ Midpoint of range of TC values associated with harvesting grapes (Dong et al. (1992))

van Hemmen et al. (2002)

Conclusions

REIs should be set at 8 days for ornamentals and raspberries, 2 days for cotton, and 1 day for other crops. Persons re-entering and/or re-handling treated crops at prior intervals should wear cotton overalls buttoned at the neck and wrist (or equivalent clothing) and chemical-resistant gloves.

2.7 First Aid Instructions

When the current review commenced, First Aid Instructions for carbaryl when present at more than 12% were as follows:

CODE	FIRST AID INSTRUCTION
a	If poisoning occurs, contact a doctor or Poisons Information Centre. Phone Australia 131 126
h	If swallowed, give one atropine tablet every 5 minutes until dryness of the mouth occurs—if poisoned by skin absorption or through lungs, remove any contaminated clothing, wash skin thoroughly and give atropine tablets as above. Get to a doctor or hospital quickly

First Aid Instruction '**h**', which relates to the treatment of anti-ChE poisoning with atropine following oral, dermal and inhalational exposure has now been deleted from the FAISD Handbook and replaced with the following instruction, which also incorporates the Poisons Information Centre contact details in instruction '**a**':

CODE	FIRST AID INSTRUCTION
m	If swallowed, splashed on skin or in eyes, or inhaled, contact a Poisons Information Centre (phone Australia 131 126) or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. If swallowed, activated charcoal may be advised. Give atropine if instructed.

Therefore, First Aid Instructions '**a**' and '**h**' should be removed from the labels of products containing more than 12% carbaryl and replaced with statement '**m**'.

2.8 Safety Directions

800 g/kg WP

The OCS has concluded that persons mixing/loading carbaryl 800 g/kg WP products are likely to incur unacceptable levels of exposure (Section 5.2, scenario 1). The estimated extent of dermal exposure is so high that a combination of gloves and chemical-resistant clothing will not afford sufficient protection to a mixer/loader working at the anticipated daily rate. The OCS recommends that carbaryl WP products should be presented in WSP, and Safety Directions will be same as for SC products as presented below.

500 g/L SC

Based on the properties of their individual constituents, carbaryl 500 g/L SC products are anticipated to be of moderate oral and low dermal and inhalational acute toxicity. They are expected to be slight skin and eye irritants, and to have low dermal sensitisation potential. Appropriate Warning Statements for skin and eye irritation are required. Due to the potential for dermal irritation and unacceptable dermal exposure to carbaryl when preparing and applying the spray mixture (Section 5.2, scenarios 2 and 3), gloves and overalls should be worn. The following new entry should be placed in the FAISD Handbook:

WD (WATER-SOLUBLE PACKAGING) 800 g/kg OR LESS AND SC 500 G/L OR LESS	
Product is poisonous if absorbed by skin contact or swallowed.	120 130 131 133
Will irritate the eyes and skin.	161 162 164
Avoid contact with eyes and skin.	210 211
Obtain an emergency supply of atropine tablets 0.6 mg.	373
When opening the container, preparing spray and using the prepared spray, wear cotton overalls buttoned to the neck and wrist and a washable hat and elbow-length PVC gloves.	279 280 281 282 290 292a 294
After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.	350
After each day's use, wash gloves and contaminated clothing.	360 361 366

37 g/kg soap bar

Based on the properties of the individual constituents, the product is expected to be of very low acute oral toxicity. The acute dermal and inhalational toxicity of this product cannot be accurately extrapolated but are expected to be low or very low. Based on the irritant properties of the individual ingredients in the formulation, it is expected to exhibit nil to slight skin and eye irritation potential. There is no evidence that Joseph Lyddy G-Wizz Insecticidal Dry Shampoo for Horses and Ponies would be a skin sensitiser.

This review recommends the inclusion of a new entry in the FAISD Handbook to encompass the product, with the title of '**BAR 40 g/kg or less**'. Although the acute toxicological hazards of the product are expected to be low, there is potential for toxicologically unacceptable exposure to carbaryl via the dermal route, and operators should wear overalls and gloves when applying it. Any likely inhalation hazards will be minimised by including a dust inhalation Warning Statement.

BAR 40 g/kg OR LESS	
Product is poisonous if absorbed by skin contact, inhaled or swallowed.	120, 130, 131, 132, 133
May irritate the eyes and skin.	160, 162, 164
Avoid contact with eyes and skin.	210, 211
Do not inhale dust.	220, 221
When using the product wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and rubber gloves.	279, 283, 290, 292b, 312
After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.	350
After each day's use, wash gloves.	360, 361

2 g/L lotion with 20 g/L sulfur and 50 g/L zinc oxide

Joseph Lyddy Y-Itch Animal Insecticide Bactericide is applied to the skin of dogs and horses for ectoparasite control. By extrapolation from the toxicological characteristics of the individual constituents, the product is expected to have low to very low acute oral and dermal toxicity, slight skin and eye irritancy, to be a potential respiratory tract irritant and to be a potential dermal sensitiser. Appropriate Warning Statements for skin, eye and respiratory tract irritation and skin sensitisation are therefore required. The acute inhalational toxicity of the product cannot be accurately extrapolated due to lack of data for some of its individual constituents. However, as formulated and used, the product would exhibit very low potential for inhalation toxicity. There is potential for extensive dermal contact with the product because it is applied manually and massaged in to the fur coat after application. Hence, there is a requirement for gloves to be worn when using the product. These should be made of neoprene, nitrile or butyl rubber, as recommended by the manufacturer of the non-active constituent which constitutes the majority of the formulation. The following new entry should be placed in the FAISD Handbook:

LOTION 2 G/L OR LESS WITH SULFUR 20 G/L OR LESS AND ZINC OXIDE 50 G/L OR LESS	
Product is poisonous if absorbed by skin contact or swallowed.	120, 130, 131, 133
May irritate the eyes, nose and throat and skin.	160, 162, 163, 164
Repeated exposure may cause allergic disorders.	180
Avoid contact with eyes and skin.	210, 211
Do not inhale vapour.	220, 222
Ensure adequate ventilation during use.	272
When opening the container and using the product wear elbow-length neoprene, nitrile or butyl rubber gloves.	279, 280, 283, 290, 295
After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water.	350
After each day's use, wash gloves.	360, 361

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