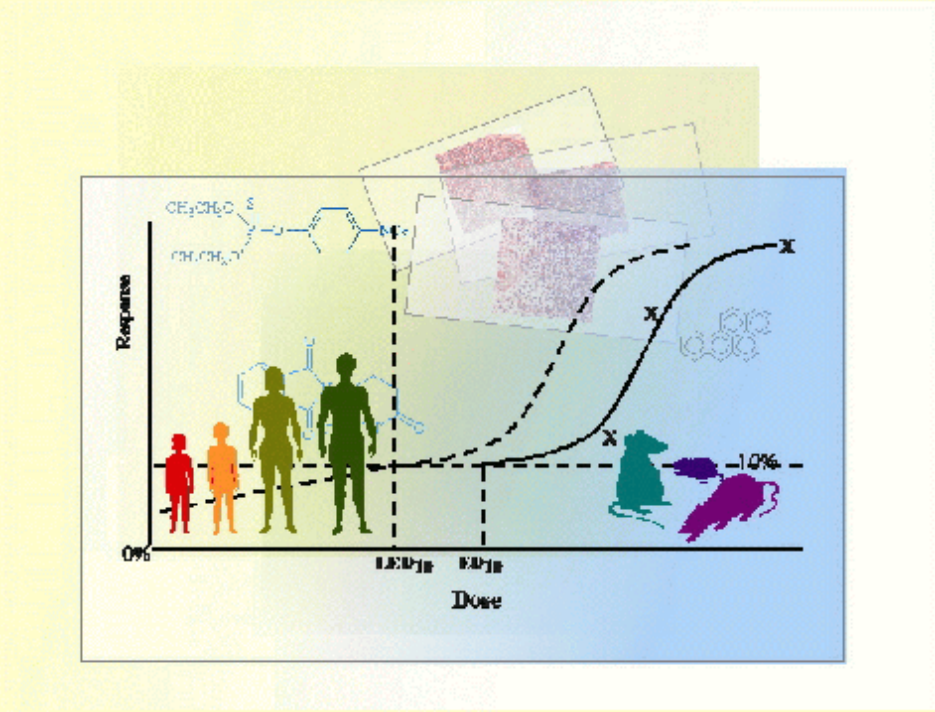
ESTIMATION OF CUMULATIVE RISK FROM N-METHYL CARBAMATE PESTICIDES:

Preliminary Assessment



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division
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Preliminary N-Methyl Carbamate Pesticides Cumulative Assessment Technical Executive Summary

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By 2006, under Federal law, EPA must review the safety of all existing tolerances (maximum residue allowed on a food) that were in effect as of August 1996. The law requires EPA to place the highest priority for tolerance reassessment on pesticides that appear to pose the greatest risk, such as the N-methyl carbamate pesticides (NMCs) class of pesticides. Over the last several years, the Office of Pesticide Programs (OPP) has been conducting risk assessments for individual NMC pesticides and where necessary, has implemented mitigation measures to reduce exposure to these pesticides. As part of the tolerance reassessment process under the Food Quality Protection Act (FQPA) of 1996, EPA must consider available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity. A cumulative risk assessment also incorporates exposure data from multiple pathways (i.e., food, drinking water, and residential/non-occupational exposure to pesticides in air, or on soil, grass, and indoor surfaces).

EPA has completed the preliminary cumulative risk assessment for the N-methyl carbamate pesticides (NMCs). This assessment is the second cumulative risk assessment performed under the FQPA. This methodology was first developed and reviewed several years ago with the cumulative assessment performed for the organophosphorous pesticides. The Agency's methods result in well developed measurements of the probability of exposure to more than one NMC pesticide. Due to the preliminary nature of this assessment, it is too soon to draw firm conclusions about risks or consider risk management possibilities. Risk mitigation measures have already been taken on some individual members of this group of pesticides through interim reregistration decisions. The individual chemical assessments for other members of this group have not yet been completed. EPA continues to have confidence in the overall safety of our food supply and emphasizes the importance of eating a varied diet rich in fruits and vegetables. NMC residues in drinking water may be a concern in very limited, specific, and identifiable regions of the country, but in the majority of places do not appear to contribute substantially to exposure. Crack and crevice and pet collar uses are the only remaining indoor uses of the NMC.

The cumulative assessment of risks posed by exposure to multiple chemicals by multiple pathways presents a formidable scientific challenge. To meet this challenge, EPA began developing new tools and methods for conducting cumulative risk assessments on pesticide chemicals shortly after the enactment of FQPA. EPA has relied on the FIFRA Scientific Advisory Panel (SAP) to peer review guidance documents, methods, approaches, and pilot analyses to ensure that EPA is using appropriate methods and sound science. The SAP has recognized and reacted favorably to the EPA's methods development. In addition to the SAP reviews, EPA has sought and considered public comments on these approaches.

There are many steps involved in quantitatively assessing the potential human risk associated with the N-methyl carbamate (NMC) pesticides. Several key steps include:

- ❑ Selection of the pesticides, pesticide uses, routes, and pathways from the full group of NMCs with exposure and hazard potential to include in the quantitative estimates of risk;
- ❑ Determination of the relative toxic contribution of each NMC, selection of an index chemical to use as the point of reference to standardize the toxic potencies of each NMC, and establishment of a value to estimate potential risk for the group;
- ❑ Estimation of the risks associated with all pertinent pathways of exposure in a manner that is both realistic and reflective of variability due to differences in location, time and demographic characteristics of exposed groups;
- ❑ Identification of the significant contributors to risk; and
- ❑ Characterization of the confidence in the results and the uncertainties encountered in the assessment.

The complex series of evaluations involved hazard and dose-response analyses, assessments of food, drinking water, and residential/non-occupational exposures, and risk characterization. The approach to each of these components and their results is briefly explained below.

A cumulative risk assessment begins with the identification of a group of chemicals, called a common mechanism group (CMG), that induce a common toxic effect by a common mechanism of toxicity. Pesticides are determined to have a "common mechanism of toxicity" if they act the same way in the body--that is, the same toxic effect occurs in the same organ or tissue by essentially the same sequence of major biochemical events. The NMC pesticides share a common mechanism of toxicity and are the second common mechanism group identified by EPA. The inhibition of acetylcholinesterase by carbamylation of the serine hydroxyl group located in the active site of the enzyme is the common effect for the NMC pesticides. Acetylcholinesterase is an enzyme that regulates a neurotransmitter, acetylcholine. If acetylcholinesterase is inhibited by NMC exposure, the nerve impulses remain active too long and overstimulate the nerves and muscles.

Once a common mechanism group is identified, it is important to determine what chemicals from that group should be included in the quantification of cumulative risk. In choosing the specific NMC pesticides to be included in the cumulative risk assessment, EPA considered risk mitigation decisions and exposure potential. There are ten cholinesterase-inhibiting NMC pesticides considered in this preliminary cumulative assessment (see Table ES.1). EPA identified three exposure pathways of interest: food, drinking water, and residential/ nonoccupational for these pesticides. Each of these pathways was initially evaluated separately, and, in doing this step of the

analysis, EPA determined which of the NMCs were appropriately included for a particular pathway. The cumulative assessment of potential exposure to NMCs in food includes nine NMC pesticides that are currently registered in the U.S. or have import tolerances. The preliminary assessment of the residential exposure pathway considers only three NMCs (propoxur, carbaryl, and methiocarb) registered in the U.S. for home use. The current assessment reflects the most up-to-date or best available residential use picture for these chemicals. Specifically, the residential assessment did not consider post-application exposure resulting from liquid broadcast treatments to lawns since this use is currently under mitigation.[1] Based on usage patterns, seven NMC pesticides were considered in the cumulative water exposure assessment.

EPA used the relative potency factor (RPF) method to determine the joint risk associated with exposure to these NMCs. Briefly, the RPF approach uses an index chemical as the point of reference for comparing the toxicity of the NMC pesticides. Relative potency factors (i.e., the ratio of the toxic potency of a given chemical to that of the index chemical) are then used to convert exposures of all chemicals in the group into exposure equivalents of the index chemical. Because of its high quality dose response data for all routes of exposure, EPA selected oxamyl as the index chemical for standardizing the toxic potencies and calculating relative potency factors for each NMC. Toxic potencies for the NMCs were determined using a common endpoint derived from the same laboratory animal species and sex for all three exposure routes of interest (i.e., oral, dermal, and inhalation). Brain cholinesterase inhibition from rats measured at or near peak cholinesterase inhibition following acute, single exposure was determined to be the appropriate endpoint for estimating the relative toxic potency of each NMC. Brain cholinesterase inhibition is a direct measure of the mechanism of toxicity, and thus does not have the uncertainty associated with using blood measurements of cholinesterase inhibition, which serve as surrogates for cholinesterase inhibition in the peripheral nervous system. Furthermore, relative toxic potencies derived from brain data were generally similar to those derived from red blood cell data and showed less variability, and thus less uncertainty.

A dose-response model was used to determine relative toxic potencies of the NMC pesticides for the brain cholinesterase data oral, dermal, and inhalation routes of exposure. The points of departure for the index chemical, oxamyl, were derived using the exponential model for each route of exposure (i.e., oral, dermal, and inhalation). A point of departure is a point estimate on the index chemical's dose-response curve that is used to extrapolate risk to the exposure levels anticipated in the human population. EPA compares exposure information with the point of departure value to estimate potential risk to humans.

Three key pathways of exposure to NMC pesticides–dietary pathways of food and drinking water, and the nondietary pathway from exposure in residential and other nonoccupational settings–were included in this assessment. An important aspect of the

[1] The Preliminary NMC CRA assessed post-application exposure resulting from the granular broadcast use of carbaryl only. In absence of granular turf transferable residue (TTR) data, OPP used liquid TTR data coupled with liquid transfer coefficient data. This approach is expected to overestimate post-application exposure resulting from the granular broadcast uses of carbaryl, but is the best available data at this time.

exposure analyses is to develop exposure scenarios resulting from the uses for each NMC. Factors EPA considered in this analysis included duration, frequency, and seasonality of exposure. Evaluation of chemical use profiles allows for the identification of exposure scenarios that may overlap, co-occur, or vary between chemicals, as well as for the identification of populations of concern.

Exposures through residential uses and in drinking water are incorporated into cumulative exposure assessments on a regional basis. EPA conducted eight regional assessments for drinking water and three for residential exposures in order to account for differing agronomic uses and reflect the differences in climate, soil conditions, and resulting pest pressures across the entire U.S. Exposure to NMC pesticide residues in foods is considered to be uniform across the nation (i.e., there are no significant differences in food exposure due to time of year or geographic location). The single national estimate of food exposure was combined with region-specific exposures from residential uses and drinking water in three regions that represent the highest potential for exposure. The assumption of nationally uniform food exposure is based on the understanding that, to a large extent, food is distributed nationally and food consumption is independent of geographic region and season.

All of the hazard data (i.e., relative potency factors and points of departure), exposure data, and exposure scenarios must be combined in a manner to produce reasonable and realistic estimates of exposures likely to be encountered by the public in location and time (seasonally). EPA used three publicly available computer software models -- Calendex™, CARES™, and Lifeline™ , to integrate various pathways while simultaneously incorporating the time dimensions of the data[2]. A comparison of the food + water results from the three models is presented in the main document. These models provide a focused, detailed profile of potential exposures to individuals across a calendar year. The approach for each pathway of exposure and results for the NMC cumulative risk assessment are explained below:

Food: The food component of the NMC cumulative risk assessment is considered to be highly refined because it is based on residue monitoring data from the USDA's Pesticide Data Program, supplemented with information from the Food and Drug Administration (FDA) Surveillance Monitoring Programs and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. They also provide direct measures of co-occurrence of NMCs in the same sample, alleviating much of the uncertainty about co-occurrence in foods that are monitored in the program. PDP samples with non-detectable residues were treated in this assessment as "zero" values. Only residue data from composite samples were utilized in this assessment. For those foods not monitored in PDP, similar commodities that are measured by PDP served as surrogate data sources. This approach is considered to be reasonable and generally sound given that it is based on the concept that

[2] These software models are available at: http://www.exponent.com/practices/foodchemical/deem.html for DEEM/Calendex; at http://www.ilsi.org/info/infolist.cfm?pubentityid=12&infoid=41 for CARES; and http://www.thelifelinegroup.org/ for LifeLine. We note that this Preliminary assessment used all three models to assess exposure through the dietary route (food + water), but used only DEEM/Calendex to assess exposures through all three routes (food + water + residential)

families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns and residue levels.

Another important aspect of the food exposure assessment is that it is based on actual consumption data from the USDA's Continuing Survey of Food Intakes by Individuals, 1994-1996 / 1998 (CSFII). The CSFII provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year and across all 50 states. In this survey, 20,607 individual participants were interviewed over two discontinuous days. The data were supplemented by the 1998 survey of 5,559 additional children from birth through 9 years old. For this preliminary assessment, the following age groups were analyzed: 1 and 2 year olds (i.e, 1 to < 3 years of age); 3 through 5 year old (i.e., 3 to <6 years of age); 20 through 49 year olds (i.e., 20 to <50 years of age); and 50 years of age and greater. These age groups were selected because other age groups are rarely shown to be the most highly exposed in single-chemical assessments. EPA plans to perform additional analyses as part of the revised cumulative assessment before reaching specific conclusions about risks associated with exposure to NMCs via food. The data inputs and assumptions need to be verified, and the results at the tail end of the distribution at the higher percentiles of exposure for children's age groups need to be evaluated to ensure they reflect reasonable consumption patterns. Additionally, EPA is in the process of conducting sensitivity analyses that will permit a fuller characterization of the contributors or sources of potential risks associated with the food pathway.

Water: The drinking water assessment focuses on areas where combined NMC exposure is likely to be among the highest within each region as a result of total NMC usage and vulnerability of drinking water sources. This analysis is based on a probabilistic modeling approach that considers the full range of data and not a single high-end estimate. Exposures in drinking water to individuals are incorporated into the cumulative exposure assessment on a regional- and source water-specific basis (i.e., ground water and surface water, by region). The regional drinking water exposure assessments are intended to represent exposures from vulnerable drinking water sources resulting from typical NMC usage and reflect seasonal variations as well as regional variations in cropping and NMC use. Each regional assessment focuses on areas where combined NMC exposure is likely to be among the highest within the region as a result of total NMC usage, adjusted for relative potencies, and vulnerability of the drinking water sources. For ground water, shallow private wells in highly permeable soil and vadose zone materials are expected to be most vulnerable. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable. The co-occurrence of NMC residues in water is primarily estimated from modeling. Monitoring data are not available consistently enough to be the sole basis for the assessment. However, monitoring data are used to corroborate the modeling results and have helped confirm locations of potentially vulnerable drinking water sources.

In most of the country, NMC residues in drinking water sources are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure. However, NMC residues estimated for vulnerable private wells in some areas of Florida (primarily along the central ridge) and the southeastern coastal plain are major contributors to the cumulative NMC exposures. These areas represent what the Agency believes to be the most vulnerable private well drinking water sources for the NMCs based on available monitoring, current use patterns, and known soil and hydrologic conditions. In those vulnerable areas, which represent a relatively small area of the country, the estimated ground water residues are reasonable estimates of drinking water exposure for residents who get their drinking water from shallow private wells.

Residential: Applications of NMC pesticides in and around homes, schools, offices, and other public areas may result in potential exposure via the oral (due to hand-to-mouth activity by children), dermal, and inhalation routes. There are only three NMC chemicals with currently registered residential uses and these were considered in the residential/non-occupational exposure pathway assessment. The current assessment is based on a probabilistic approach. Several reliable data sources were used to define how pesticides are used, dissipation of pesticide residues, how people may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn). Like drinking water, the residential exposure assessment is conducted on a regional basis and focused on the South (where use practices are expected to result in higher exposures than the rest of the U.S.) and also reflects seasonal variations. In particular, for the three routes considered in the residential assessment exposure from hand-to-mouth activity by children and through the dermal route appears to be the most significant contributors to the risk. However, EPA notes that there are significant conservatisms incorporated into the assessment of exposure through these exposure pathways/routes and, as part of the revised assessment, we expect to revise this portion of the assessment considering any advice and suggestions provided by the SAP.

Finally, it is important to re-iterate that this is a preliminary assessment and interpretation of results needs to be done with care. The current assessment does not incorporate extrapolation, uncertainty, and safety factors for the individual NMC pesticides. Furthermore, EPA has not reached a decision as to the percentile of distribution to be used for regulatory purposes. In short, interpretation of the risk estimates presented in this preliminary CRA depends upon the synthesis and processing of a vast body of data on hazard and exposures and no single value in the assessment should be used to independently arrive at the interpretation of the risk estimates or results.

At the present time, EPA believes that the preliminary cumulative risk assessment for the NMCs represents the state of the science regarding existing hazard and exposure data and the models and approaches used. EPA expects to make revisions in the coming months based on comments from the public and from the FIFRA

SAP meeting planned for August, 2005. EPA also expects to include decisions regarding extrapolation and safety factors in the revised cumulative risk assessment.

Table ES.1. *N*-methyl Carbamate Pesticides Considered in the Preliminary Cumulative Risk Assessment

Pesticide	Pesticide Pathways		
	Food Exposure	Drinking Water Exposure	Residential Exposure
Carbaryl	√	√	√
Aldicarb	√	√	
Oxamyl	√	√	
Formetanate HCl	√	√	
Methomyl	√	√	
Carbofuran	√	√	
Propoxur	√		√
Methiocarb	√		√
Thiodicarb	√	√	
Pirimicarb	√		

List of Acronyms

AChE	Acetycholinesterase
BMD	Benchmark dose
BMDL	Lower limit on the benchmark dose
ChE	Cholinesterase
CRA	Cumulative Risk Assessment
CSFII	USDA's Continuing Survey of Food Intake by Individuals
DEEM-FCID	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
EFED	Environmental Fate and Effects Division
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, Rodenticide Act
FQPA	Food Quality Protection Act
FR	Federal Register
LCO	Lawn Care Operator
LOAEL	Lowest Observable Adverse Effect Level
LOQ	Limit of Quantification
MOE	Margin of Exposure
MRID	Master Record Identification Number
NASS	National Agricultural Statistics Survey
NHGPUS	National Home and Garden Pesticide Use Survey
NMC	N-Methyl Carbamate
NMC CRA	N-Methyl Carbamate Cumulative Risk Assessment
OP CRA	Organophosphorus Pesticide Cumulative Risk Assessment
OPP	The EPA's Office of Pesticide Programs
ORETF	Outdoor Residential Exposure Task Force
PCO	Pest Control Operator
PDP	Pesticide Data Program (USDA)
PoD	Point of Departure
PRZM-EXAMS	Pesticide Root Zone Model- Exposure Analysis Modeling System
REJV	Residential Exposure Joint Venture
RPF	Relative Potency Factor
SAP	Scientific Advisory Panel
SOP	Standard Operating Procedure
TDS	Total Diet Study
TTR	Turf Transferable Residues
UE	Unit Exposure

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I. Preliminary N-Methyl Carbamate Cumulative Risk Assessment

A. Introduction

The passage of the Food Quality Protection Act (FQPA) in August 1996 required EPA to consider available information concerning the combined toxic effects to human health that may result from dietary, residential, or other non-occupational exposure to chemicals that have a common mechanism of toxicity (i.e., cumulative risk). In developing the methodology for cumulative risk assessment, the Agency developed guidance documents for determining whether two or more chemicals share a common mechanism of toxicity, *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity* (USEPA, 1999a) and for conducting cumulative risk assessment, *The Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (USEPA, 2002a).

Based on the principles contained in the above guidance documents, the first cumulative risk assessment developed by the Agency was for the organophosphorus (OP) class of pesticides. EPA completed a revised cumulative risk assessment for these pesticides in June 2002 (USEPA, 2002b). In this assessment, OPP developed and demonstrated in detail the methods, parameters, and issues that should be considered in estimating cumulative risk associated with common mechanism pesticides by multiple pathways of exposure. Various aspects of the hazard and dose-response assessment and the exposure analyses were presented to both the SAP and the public for comment numerous times over the course of several years. Both the SAP and the public provided helpful and insightful comments and ideas which were incorporated into the revised documents.

There are a number of steps involved in quantitatively assessing the potential human risk associated with the N-methyl carbamate pesticides. The complex series of evaluations involve hazard and dose response analyses; assessments of food, drinking water, and residential/non-occupational exposures; and risk characterization. Several key steps include:

1. Selecting a Common Mechanism Group (CMG) of chemicals that produce a common toxic effect(s) by a common mechanism of toxicity.

2. Selection of a subset of CMG chemicals as a Common Assessment Group (CAG) for which the cumulative risk assessment will be performed. This includes selection of pesticides and pesticide uses, routes, and pathways from the full common mechanism group with sufficient exposure and hazard potential to include in the quantitative estimates of risk.

3. Determination of the relative toxic contribution of each N-methyl carbamate in the CAG; selection of an index chemical to use as the point of reference to standardize the toxic potencies of each N-methyl carbamate; and establishment of a baseline (or reference) value to use to estimate potential risk for the group;

4. Estimation of the risks associated with all pertinent pathways of exposure in a manner that is both realistic and reflective of variability due to differences in location, time, and demographic characteristics of the exposed groups;

5. Identification of the specific scenarios which contribute to risk and development of a quantitative estimate of these exposures and risks;

6. Characterization of the confidence in the results and their uncertainties.

Steps 1 and 2 are briefly described below. This preliminary risk assessment focuses on steps 3-6.

In 2001, EPA concluded that the N-methyl carbamate pesticides share a common mechanism of toxicity. This Common Mechanism Group (CMG)[3] was established based on the shared structural characteristics and similarity and their shared ability to inhibit acetylcholinesterase (AChE) by carbamylation of the serine hydroxyl group located in the active site of the enzyme (USEPA, 2001a). For this group of pesticides, following maximal inhibition of cholinesterase (ChE), recovery typically occurs rapidly (minutes to hours). In a February 4, 2004 Federal Register Notice, EPA announced the members of the Common Assessment Group (CAG)[4]. These ten carbamates all display ChE-inhibiting activity, have current active registrations, and are expected to contribute to the carbamate cumulative risk through quantitatively meaningful exposure scenarios. The ten members of the CAG for the N-methyl carbamates and those chemicals which are included in the quantitative cumulative risk assessment are listed in Table I.A.1 along with the pathways are routes which are assessed.

[3]A Common Mechanism Group (CMG) is a defined as a group of two or more chemicals which display a Common Mechanism of Toxicity. That is, they cause a common toxic effect to human health by the same, or essentially the same, sequence of major biochemical events. A more detailed description of this can be found in the background document to the December 3, 2004 Scientific Advisory Panel and in the document *Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity* (USEPA, 1999a).

[4]A Cumulative Assessment Group (CAG) is a subset of the CMG for which the Cumulative Risk Assessment will be performed. This CAG may not include all chemicals grouped by a common mechanism of toxicity since not all chemicals in the CMG should be included in the quantitative cumulative risk assessment due, e.g., to low hazard potential or the existence of only minor exposure scenarios.

Table I.A.1 Summary Information Regarding the NMC pesticides and the Uses, Routes, and Pathways included in the Preliminary NMC CRA

Pesticide	Pesticide Uses	Pesticide Pathways			Pesticide Routes		
		Food	Drinking Water	Residential	Oral	Dermal	Inhalation
Carbaryl	Ag crops	X	X		X		
	Lawn			X	X	X	X
	Garden			X		X	X
	Ornamentals			X		X	X
	Fruit Trees			X		X	X
	Pet collar			X	X	X	
	Golfer exposure			X		X	
Aldicarb	Ag crops	X	X		X		
Oxamyl	Ag crops	X	X		X		
Formetanate HCl	Ag crops	X	X		X		
Methomyl	Ag crops	X	X		X		
Carbofuran	Ag crops	X	X		X		
Propoxur	Ag crops	X			X		
	C&C			X	X	X	X
	Pet collars			X	X	X	
Methiocarb	Ag crops	X			X		
	Ornamental			X		X	X
Thiodicarb	Ag crops	X	X		X		
Pirimicarb	Ag crops	X			X		

The cumulative risk assessment guidance describes key principles for conducting these risk assessments. One such principle is the need to consider the time frame of both the exposure (e.g., When does exposure occur? What is the exposure duration?) and of the toxic effect (e.g., What are the time to peak effects and the time to recovery? How quickly is the effect reversed?). Both should be adequately considered so that an individual's exposure is matched with relevant and appropriate toxicological values in terms of duration and timing. ChE inhibition caused by the N-methyl carbamates is followed by rapid recovery within minutes to hours. This rapid recovery is a unique characteristic of this group of pesticides which needs consideration and characterization. Cumulative risk assessments should also account for temporal aspects of exposure such as those related to the time of year during which applications resulting in exposures are likely to occur, the frequency of application and period of re-application. Moreover, these assessments must appropriately consider age-dependant and demographic factors and patterns. The ways in which the Agency has approached each of these challenges in its cumulative hazard, exposure, and risk assessments is described throughout the document.

It should be noted that the cumulative assessment is intended to serve as a pointer toward major sources of risk likely to accrue due to the use of a variety of pesticides with a common mechanism of toxicity, with regulatory decision making based

upon the many detailed aspects of the single-chemical, aggregate risk assessment. Because of the requirement that many data sets be combined into a single assessment, reducing the likelihood of compounding conservative assumptions and over-estimation bias becomes very important in constructing the cumulative risk assessment. As a result, OPP has chosen to work with those data which most closely reflect likely exposures and not to incorporate those data which are inherently conservative by their nature (e.g., field trial data which incorporate maximum application rates and minimum pre-harvest intervals).

A meeting of the FIFRA SAP was held in February, 2005 which covered a variety of issues regarding hazard assessment, pharmacokinetic modeling of carbaryl, drinking water exposure modeling and a case study exposure assessment including surface water, food, and residential exposure assessment. EPA has considered the SAP's advice and recommendations provided in February, 2005 and from previous meetings of the FIFRA SAP focused on cumulative risk assessment in the current assessment. Furthermore, EPA has considered comments from the public provided during the development of the OP cumulative risk assessment in developing this assessment for the N-methyl carbamate class of pesticides. As such, the preliminary cumulative risk assessment for the N-methyl carbamates reflects the current state of the science regarding data availability and model development. EPA will present the preliminary cumulative risk assessment to the FIFRA SAP in August, 2005. The revised cumulative risk assessment is expected to be released at a later date.

The current document is presented in two major parts:

- Part I: Preliminary cumulative risk assessment
- Part II: Appendices which provide background material, additional graphs, and more technical and/or extensive details surrounding the analyses contained in Part I

Part I is divided into 11 sections. Section A is this general introduction. The following section, Section B, presents the Hazard Assessment with specific discussion of the Relative Potency Factor approach and empirical dose-response and time course modeling used to estimate relative potency. The next three sections (Sections C, D, and E) focus on each of the major exposure pathways (food, drinking water, and residential, respectively) including a discussion of assumptions, data inputs, and inter-relationships of exposure data. Each of these pathways has unique issues relating to availability of data, scale, and interpretation of results. Results of each aspect of the assessment are discussed in these sections with particular attention given to how they reflect potential exposures to the population and what might be inferred with regard to significant exposure pathways/scenarios. Section F of the document examines the results of combining estimates of risk from all sources of exposure (a probabilistic cumulative assessment) and further discusses the interpretation of the outputs with respect to identification of the most significant pathways and scenarios. The results in this section were generated by the DEEM/Calendex software. Additional analyses which focus on the most exposed subpopulations were performed with the LifeLine and CARES software, and a comparison of results between the three exposure models is

presented in Section G of the document. The next section (Section H) of this document is the risk characterization part which further discusses and characterizes the inputs to the assessment as well as the resulting model exposure estimates. Section I of this document provides summary information regarding planned future activities and next steps with respect to production of the revised cumulative risk assessment. The final section of Part I of this document is Section J. which provides references for the material cited in Parts A through I.

I. Preliminary NMC Cumulative Risk Assessment

B. Hazard/Relative Potency Factors

1. Introduction

OPP designated the *N*-methyl carbamate (NMC) pesticides as a common mechanism group (USEPA, 2001a) based on the shared structural characteristics and similarity and their shared ability to inhibit acetylcholinesterase (AChE) by carbamylation of the serine hydroxyl group located in the active site of the enzyme. Following maximal inhibition of cholinesterase, recovery typically occurs rapidly (minutes to hours). At the February 2005 meeting of the FIFRA SAP, EPA presented the status of three key science activities involving the cumulative hazard characterization of the NMCs. The areas discussed at the February 2005 meeting included methods for measuring cholinesterase inhibition caused by NMCs, empirical dose-response methods proposed for quantifying chemical potency, and physiologically based pharmacokinetic modeling (PBPK) for carbaryl. EPA has considered the comments from the SAP in the development of the current preliminary NMC cumulative risk assessment. As discussed by EPA at the February 2005 SAP meeting, pharmacokinetic data are only available for one NMC-- carbaryl-- at this time. As such, the data are not available to develop a multi-chemical, multi-pathway PBPK model for the NMC cumulative risk assessment (See Appendix II.B.6). Therefore, the current preliminary cumulative risk assessment relies on the relative potency factor (RPF) method for quantifying chemical potency. In the RPF approach, the toxic potency of each chemical is determined. A member of the cumulative assessment group (CAG) is selected as the index chemical which is used as the point of reference for standardizing the cholinesterase inhibiting potency of the other chemical members of the CAG. This cumulative hazard assessment represents the collaborative efforts of scientists from OPP and EPA's National Health and Environmental Effects Research Laboratory (NHEERL) and National Center for Computational Toxicology (NCCT).

The purpose of this chapter is to describe EPA's approach for:

- ❑ Determination of the relative cholinesterase inhibiting potency and time to recovery for each *N*-methyl carbamate in the CAG;
- ❑ Selection of the index chemical to use as the point of reference to standardize the potencies of each *N*-methyl carbamate;
- ❑ Establishment of a baseline or reference value (i.e., points of departure) to use to estimate potential risk for the group for each route of interest and;
- ❑ Improvement of the cumulative risk assessment methodologies.

2. Endpoints and Toxicology Studies

When using the RPF method and before the cumulative risk of exposure to the NMCs can be quantified, the relative toxic potency of each NMC must first be determined. The determination of relative toxic potency should be calculated using a uniform basis of comparison, by using, to the extent possible, a common tissue and species, and sex for all the exposure routes of interest (USEPA, 2002a). NMCs exert their neurotoxicity by carbamylating the enzyme acetylcholinesterase (AChE) in both the central (brain) and peripheral nervous systems. Since cholinesterase inhibition is the critical event in NMC toxicity, ChE inhibition provides the common endpoint for the preliminary cumulative risk assessment. Behavioral changes in animal studies usually occur at equal or higher doses compared to doses needed to inhibit cholinesterase activity. Moreover, behavioral measures may be limited in terms of the scope of effects assessed and by the lack of standardization of laboratory equipment among laboratories. Thus, the available ChE activity measures provide a more uniform measure of toxicity for performing cumulative risk assessment. In order to evaluate the concordance between ChE inhibition and behavioral endpoints, EPA has performed a series of dose-response and time course studies with seven NMCs where RBC and brain ChE were measured along with clinical signs ('tox' score) and motor activity were measured (Appendix II.B.5; Moser et al. 2005). At present time, the analysis of the behavioral data from EPA's experiments is preliminary in nature.

There are laboratory animal data on NMCs for cholinesterase activity in plasma, red blood cell (RBC), whole blood, and brain (whole brain and brain sections). Measures of ChE inhibition in the peripheral nervous system (PNS) are very limited for ChE inhibiting pesticides, in general. As a matter of science policy, blood cholinesterase data (plasma and RBC) are considered appropriate surrogate measures of potential effects on PNS acetylcholinesterase activity, and of potential effects on the central nervous system (CNS) when brain ChE data are lacking (USEPA, 2000a). Furthermore, when RBC ChE data are of adequate quality, as is the case for the NMCs, RBC ChE data are preferred over plasma ChE data. ChE is the target enzyme for this common mechanism group and is the primary form of ChE found in RBCs. Butrylcholinesterase (BChE) is the primary form found in plasma; BChE is considered a measure of exposure but has not been shown to be of toxicological significance. Some studies with NMCs provided whole blood ChE. Whole blood ChE represents a mixture of plasma and RBC ChE, and thus may not provide a uniform endpoint for comparison across chemicals. Whole blood ChE data were not used in this assessment. In the case of brain ChE inhibition, data are available for each NMC with whole brain (or half brain). In some studies, brains were dissected into different brain areas (e.g., cerebellum). Because the brain dissections provided are not standardized across the studies and brain section data are not available for each NMC, these data do not represent a uniform basis of comparison. *RBC and brain (namely whole, half) ChE inhibition were considered potential endpoints for extrapolating risk to humans in the preliminary NMC cumulative risk assessment.*

Humans may be exposed to the NMCs through food, drinking water, in and around residences, schools, commercial buildings, etc. Therefore, the potency of NMCs needs to be determined for the oral, dermal, and inhalation routes of exposure. Under FIFRA, toxicity studies in various species (e.g., dog, mouse, rat, and rabbit) are submitted to OPP. For the NMCs, toxicity studies in the rat provide the most extensive and robust database of ChE inhibition data. Thus, the focus of this analysis was on ChE activity data derived from male and female (non-pregnant) rats. EPA used rabbit studies for pesticides with residential/nonoccupational exposure potential when dermal toxicity data in rats were not available.

Toxicological characteristics of the NMCs involve maximal ChE inhibition followed by the rapid recovery, typically in minutes to hours. As such, the critical duration of exposure for this common mechanism group is acute ChE inhibition measured at the peak time of effect. Characterizing chemical specific recovery is critical for characterizing overlapping exposures and thus cumulative risk. EPA has compiled data from several different kinds of studies:

1. oral (gavage) studies quantifying the relationship between maximum inhibition from single or multiple administered dose(s) in rat;

2. oral (gavage) studies quantifying the *in vivo* recovery time course, usually at several doses, and beginning at or around the time of maximum inhibition (which had typically been determined in preliminary studies) in rat;

3. combinations of 1 or 2 ;

4. for those pesticides with residential exposure, inhalation and dermal studies.

Data included in the preliminary cumulative risk assessment were extracted from studies submitted by pesticide registrants and from dose-response and time course studies performed by EPA's NHEERL. Table I.B.1 provides the list of various types of studies included in the analysis.

Table I.B.1. Test guidelines/studies that contain evaluations for ChE activity.

Study Type	Guideline Type
Oral	
Acute oral toxicity study in rat	OPPTS 870.1000
Acute neurotoxicity in rat	OPPTS 870.6200a
Subchronic neurotoxicity in rat	OPPTS 870.6200b
Developmental neurotoxicity oral in rat	OPPTS 870.6300
Chronic oral toxicity in rat	OPPTS 870.4100
Range finding oral toxicity study in rat	Not applicable
Other/Special Studies	Not applicable
Dermal	
21/28-Day dermal toxicity in rat or rabbit	OPPTS 870.3200
Inhalation	
Acute inhalation in rat	OPPTS 870.1200
Chronic inhalation in rat	OPPTS 870.4100

In toxicology studies submitted to EPA for pesticide registration, measurements of cholinesterase inhibition are typically performed using some variation of the Ellman spectrophotometric method (Ellman *et a*l., 1961). Under standard conditions, this method usually involves extensive sample dilution, prolonged incubation, and temperatures around 37ºC; all promote reversal of the enzyme inhibition. If precautions are not taken to prevent recovery using this method, then reported cholinesterase activities can underestimate actual cholinesterase inhibition (Winteringham and Fowler, 1966; Williams and Casterline, 1969; Nostrandt et al., 1993; Hunter et al., 1997) which could have an impact on the relative potency estimates. A radiometric method such as that reported by Johnson and Russell (1975) provides the most appropriate method for measuring cholinesterase inhibition due to NMC exposure because factors which promote reversibility are minimized. The dilution is minimized (1:30 vs. more than 1:1000 dilution for the standard Ellman method), and incubation time may be more rapid for the radiometric method (one to three minutes compared to 10 minutes or greater). Furthermore, the radiometric method may be conducted at lower temperatures. The Ellman method can be modified to minimize conditions promoting reactivation. Reducing the tissue dilution, shortening the time, and lowering the temperature of the assay all limit the amount of

spontaneous decarbamalyation of the inhibited enzyme (Nostrandt et al., 1993). Although modifications to the Ellman method are not standardized, when performed with the appropriate care, the modified Ellman method can provide reliable cholinesterase data.

To aid in the characterization of the cholinesterase data provided by the studies submitted for registration, scientists from EPA's NHEERL have systematically evaluated cholinesterase inhibition following acute exposures of adult rats to seven *N*-methyl carbamates (carbaryl, carbofuran, formetanate HCl, methomyl, methiocarb, oxamyl, propoxur) using both the standard Ellman and radiometric techniques. The results of these experiments were presented to the FIFRA SAP in February, 2005 and at the March, 2005 meeting of the Society of Toxicology (Hunter *et al*., 2005). The data from these experiments is included in Appendix II.B.1. EPA's issue paper presented to the FIFRA SAP in February, 2005 provided graphical comparisons of the data from selected registration studies and EPA's radiometric experiments. These graphical comparisons showed good concordance between the registration data and EPA's radiometric experiments. In the current preliminary cumulative risk assessment, these data have been analyzed statistically (see section I.B.3). Overall, the results provided by the EPA radiometric studies provide similar benchmark dose estimates to the registration studies.

The laboratory protocols or standard operating procedures (SOPs) for some registration studies have been provided by the pesticide registrants. So far EPA has received protocols or SOPs for studies with oxamyl, methomyl, formetanate HCl, and carbofuran[5]. The protocols available at present time indicate that the experimental conditions among laboratories vary but that dilutions are generally limited to approximately 1:20 and that samples are frozen immediately. Although information regarding the time of sample handling is more limited, the available information suggests that reasonable precautions were taken in these studies to reduce reactivation prior to analysis. A summary of the information provided in these protocols can be found in II.B.5.

A summary of the studies and endpoints included in the Preliminary Cumulative Risk Assessment for the NMCs are provided in Table I.B.2. EPA anticipates the submission of new studies in the coming months. Studies provided to the Agency by October 1, 2005, will be incorporated in its revised cumulative risk assessment for the NMCs expected in the winter 2006.

[5] SOPs for pirimicarb were provided to EPA on 7/25/2005. The evaluation of pirimicarb SOPs will be included in the revised risk assessment.

Table I.B.2. List of toxicity studies used in the Preliminary *N*-Methyl Carbamate Risk Assessment.

Chemical	Oral		Dermal		Inhalation	
	Study ID	ChE Inhibition Data	Study ID	ChE Inhibition Data	Study ID	ChE Inhibition Data
Aldicarb	43442305	Brain, RBC	No residential uses, thus data are not needed			
	43442302	Brain, RBC				
	45079705	RBC				
	43829602	Brain, RBC				
	43829601	Brain				
	45068601[1] 45150701 MRID Pending	Brain				
Carbaryl	43845202	Brain, RBC	45630601	Brain, RBC	Data are not available	
	43845203	Brain, RBC				
	44122601	Brain, RBC				
	44393701	Brain, RBC				
	NHEERL	Brain, RBC				
Carbofuran	45675701	RBC	No residential uses, thus data are not needed			
	NHEERL	Brain, RBC				
Formetanate	NHEERL	Brain, RBC	No residential uses, thus data are not needed			
Methiocarb	NHEERL	Brain, RBC	40922301	Brain, RBC	Data are not available	
Methomyl	44472001	Brain, RBC	No residential uses, thus data are not needed			
	44487501	Brain, RBC				
	NHEERL	Brain, RBC				
Oxamyl	44254401	Brain, RBC	40827601	Brain, RBC	45155801	Brain, RBC
	44472001	Brain, RBC				
	44420301	Brain	44751201			
	NHEERL	Brain, RBC				
Pirimicarb	44485301	Brain, RBC	No residential uses, thus data are not needed			
	44233103	RBC				
	113638	Brain, RBC				
Propoxur	NHEERL	Brain, RBC	41066001	Brain, RBC	42648001	Brain, RBC
Thiodicarb	45138702	RBC	No residential uses, thus data are not needed			
	45138703	Brain, RBC				

[1]MRIDs listed here are referenced in the Aldicarb oral rat brain ChE analysis in Appendix II.B.2 as: 1) MRID Pending as Moser-1; 2) 45068601 as Moser-2; and 3) 45150701 as Moser-3.

3. Determination of Toxic Potency

As described in the guidance document for cumulative risk assessment (USEPA, 2002a), dose-response modeling is preferred over the use of NOAEL/LOAELs (i.e., no or lowest observed adverse effect levels) for determining relative toxicity potency. NOAELs and LOAELs do not necessarily reflect the relationship between dose and response for a given chemical, nor do they reflect a uniform response across different chemicals. In the present analysis, benchmark dose (BMD) modeling has been used to determine the toxic potency of the NMCs. EPA's draft BMD guidance (USEPA, 2000d) suggests that the central estimate on the BMD provides an appropriate measure for comparing chemical potency and that the lower limit on the central estimate (i.e., BMDL) provides an appropriate measure for extrapolating risk. Thus, in this cumulative risk assessment, the BMD_{10}, the central estimate, was selected as the response level for developing RPFs. The lower limit on the BMD_{10} (i.e., $BMDL_{10}$) was selected for the points of departure (PoDs). A PoD is a point estimate on the index chemical's dose-response curve that is used to extrapolate risk to the exposure levels anticipated in the human population. The 10% response level is generally at or near the limit of sensitivity for discerning a statistically significant decrease in ChE activity across the blood and brain compartments and is a response level close to the background ChE. As part of EPA's Revised Cumulative Risk Assessment for the OPs, EPA performed a power analysis of brain ChE data available for more than 30 OPs (USEPA, 2002b). The results of the analysis indicated that most studies can reliably detect 10% brain ChE inhibition. Furthermore, in studies submitted to EPA for pesticide registration, clinical signs and behavioral effects have not been shown in studies with near and/or below 10% ChE inhibition.

The following section describes the empirical dose-response modeling performed for the NMCs. BMD_{10} and $BMDL_{10}$ estimates for the NMCs are provided in Tables I.B.3 thru 5. Half-life time to recovery for each of the NMCs is provided in Table I.B.6. Detailed information about the empirical modeling for each chemical can be found in Appendix II.B.2.

a. Empirical Modeling: Dose-Time Response Model and Benchmark Dose Estimation

i. Dose-Time Response Model

Several features of the dose-time response for the *N*-methyl carbamates were to be captured in an empirical model:

- ❑ The rapid decline of ChE activity with increasing dose, perhaps after a "shoulder" at the low-dose end of the dose-response curve;
- ❑ A potential minimum level below which ChE activity will not drop, regardless of dose;

- The rapid decline of ChE activity after dosing to a minimum level which depends upon dose, then returns to the background level over a period of minutes to hours, at a rate that may also depend upon dose;

- Lack of early time points in most of the time course studies to accurately estimate the time of maximum effect, but instead start collecting data at around a previously estimated time of maximum effect.

The model described is the result of multiplying a dose-response model for inhibition that is closely related to the model that was successful at characterizing OP dose-response curves (USEPA, 2002b) and a time-course model for inhibition. Transformations of parameters were used to enforce constraints, since the statistical software used for estimating model parameters does not incorporate bounded estimation (for example, to require that half-life estimates remain positive).
The model for inhibition, before parameters were transformed to enforce constraints, is

$$g(d) = g(d; R, P, D_R, \gamma) = (1-P)\left(1 - e^{\log\left(\frac{1-R-P}{1-P}\right)\left(\frac{d}{D_R}\right)^{\gamma}}\right)$$

(Eq. 1)

where:

- d is administered dose, and is part of the data set;
- P is the minimum fraction of background ChE activity, and is constrained to fall between 0 and 1;
- R is the inhibition fraction associated with the desired benchmark dose (that is, the benchmark dose is the dose expected to yield 100×R% inhibition at the time of maximum effect), and is set to 0.10 in this analysis;
- D_R is the benchmark dose, constrained to be greater than 0.0;
- γ is a shape parameter to allow a shoulder at the low-dose end of the dose-response curve, and is constrained to be greater than 0.0.

Two different time course models were used. One time course model is the difference of two exponential functions, scaled so that the maximum is always 1:

$$h(t) = h(t;T_A,T_R) = C_0\left(e^{-\frac{\ln(2)t}{T_R}} - e^{-\frac{\ln(2)t}{T_A}}\right)$$

(Eq. 2)

where:

- T_A is the half-life of the process that results in an increase in inhibition, and
- T_R is the half-life of the process that results in a decrease in inhibition (recovery or reactivation).

The maximum of *h(t)* occurs at:

$$T^* = \frac{T_R T_A\left(\ln(T_R) - \ln(T_A)\right)}{\ln(2)(T_R - T_A)}$$

(Eq. 3)

so $C_0 = 1\Big/\left(e^{-\frac{\ln(2)T^*}{T_R}} - e^{-\frac{\ln(2)T^*}{T_A}}\right)$.

With this scaling, h(t) is symmetric in the two parameters (that is, *h(t; a, b) = h(t; b, a)*), which complicates statistical estimation unless a constraint is added to keep $T_R > T_A$. Also, many data sets require that *T** be specified (not estimated from the data), because the designs were inadequate for estimating *T**. For these reasons, it is convenient to reparameterize the model in terms of *T** and α = T_R / T_A and make sure α is constrained to be greater than 1.0.

The design of most of the time-course datasets considered in this assessment did not allow clean estimation of both T^* and α, and the reparameterization sometimes increased the difficulty of estimation. Thus, an alternative, much simpler, time-course model was used in all but one of the dose-time studies (aldicarb, brain ChE). In this simpler model, ChE activity is taken to be described by an exponential recovery time-course, beginning at a time δ after dosing. This gives the following recovery function:

$$h(t) = e^{-\frac{\ln(2)(t-\delta)}{T_R}}$$

(Eq. 4)

where:
T_R is the half-life of recovery
δ is the difference in time between dosing and the first ChE measurement.

In this model, the only parameter to be estimated is T_R.

Multiplying *g(d)* and *h(t)* together gives a function for ChE inhibition as a function of dose and time. Thus,

$$f(t, d) = A \times (1 - g(d) \times h(t))$$

(Eq. 5)

is a model for ChE activity as a function of dose and time, where *A* gives the background (that is, control) level of ChE activity.

There was no time-course data for any of the dermal and inhalation data sets, so the above model was simplified for those sets, either by setting the time course parameters to a fixed value, or by fitting a linear model to the natural logarithm of ChE activity, which is equivalent to an exponential dose-response model when the variance is proportional to the square of the mean ChE activity level (that is, the coefficient of variation is constant across doses).

The following transformations were used to ensure that parameters remained in their permitted range:

- $lA = ln(A)$, to force $A > 0$
- $lD = ln(D_R)$, to force $D_R > 0$
- $tz = -ln((1 - R - P)/P)$, to force $0 < P < 1 - R$
- $lg = ln(\gamma)$, to force $\gamma > 1$
- $lTr = ln(T_R)$, to force recovery half-life > 0 (in simplified time-course model)
- $ldT = ln(\alpha)$, to force $T_R > T_A$
- $lT_{max} = ln(T_{max})$, to force $T_{max} > 0$.

ii. Statistical Methodology

The statistical model fit to the dose or dose-time response data depended on whether the experimental design involved repeated measures (some RBC studies only) or not. The most general model fit to the ChE activity data was (for the simplified time course model), for individual j in study i, with sex $s(j)$ at time t_{ik}:

$$y_{ijk} = f(t_{ik}, d_{ij}; lA_{is(j)jk}, lD_{is(j)}, tz, lg, lTr_d, delta) + \varepsilon$$
$$\varepsilon \sim N\left(0, \sigma^2_{is(j)} \{ f(\cdots) \}^q \right)$$

When there was more than one study,

$$lD_{is(j)} \sim N\left(lD_{s(j)}, \sigma^2_D\right),$$

that is, the log BMD was taken to be normally distributed around a mean that possible differed between sexes.

When there were repeated observations on a subject,

$$lA_{is(j)jk} \sim N\left(lA_{is(j)k}, \sigma_A^2\right),$$

that is, the logarithm of individual animals background ChE activity levels were assumed to be normally distributed about a mean that varied between sexes, studies, and, when there were controls at all times, among times (this latter allows for the possibility of variation among analytic batches, if samples from the same time post dosing were analyzed as a batch).

When there were recovery time-course data available, the recovery half-life was allowed to differ among the doses for which recovery data were available. Often for a chemical, some datasets were just dose response studies conducted around the time of maximum inhibition, and others included a recovery phase, with samples taken every few hours or more frequently. In this case, the range of doses in all the studies together were grouped so that one dose with a time-course was included in each group. This allowed the estimate of recovery half-life to change with dose when the right data were available. However, often a chemical had recovery time course data for only a single dose level, so only a single recovery half-life could be estimated.

The process of estimating parameters proceeded in three steps. First, initial values for the parameters were arrived at using the R function getInitialValues() (included in the library DRUtils). This function provides a graphical interface that allows the user to quickly arrive at reasonable guesses for the parameters, and allows a few iterations of an optimization algorithm to improve those initial guesses, using ordinary least squares as an objective function. Based on these initial guesses, the degree to which it would be possible to uniquely estimate the model parameters was determined, by analyzing the condition number of the matrix of gradient of the model with respect to the model parameters, and of the matrix of (unscaled) variances and covariances of the parameters, evaluated at the data points (times, doses, sexes) in all the data sets. At this point, it was often possible to simplify the model by noticing that it was impossible to determine a unique value for, for example *tz*, because doses did not go high enough for inhibition to approach its maximum value, or the maximum level of inhibition was 100%.

The next step was to determine an appropriate model for the error variance. The options considered were either a constant variance, a constant variance that differed among studies and sexes, or a variance that was proportional to a power of the mean ChE activity level, and whose constant of proportionality varied among studies and between sexes. This was determined by fitting either a cell mean model (with indicator functions identifying individual dose X time X sex X study groups) or, more commonly, fitting the full nonlinear dose-time model using generalized nonlinear least squares (Pinheiro and Bates, 2000). In either case, likelihood ratio tests were used to identify the variance model to use (Pinheiro and Bates, 2000).

Using that variance model, a full version of the dose-time course model was fit to the data, and contrasts used to determine whether *ID* needed to differ among sexes. Pinheiro and Bates (2000) note that likelihood ratio tests for fixed effects in mixed effects models tend to reject the null hypothesis enthusiastically, whereas using contrasts to test parameter values comes close to the nominal type I error rates.

Finally, a simplified model was fit to the data, and the resulting parameter estimates used to determine the values of *ID* and *ITr* and their standard errors. BMDs were calculated as exp(*ID*), and BMDLs were calculated by exponentiating the lower end of a two-sided 90% confidence interval for *ID*.

All statistical analysis used the statistical software environment R (version 2.0.1, patched version of 2005-01-26; R Development Core Team, 2004) and its associated packages. Appendix II.B.3 and Appendix II.B.4 contain the computer code used in EPA's analysis.

b. Results: Benchmark Dose and Potency Estimation

Results of the empirical dose-response modeling are provided below. Detailed descriptions of the analysis and results of empirical dose-response modeling for each chemical are provided in Appendix II.B.2.

The BMD_{10}s for the NMCs range across approximately several orders of magnitude with aldicarb and pirimicarb representing the most and least potent pesticides, respectively, for both brain and RBC ChE inhibition. The number of studies available for analysis varies among the chemicals (Table I.B.2). At least two studies containing RBC and whole brain ChE inhibition in male and female rat were available for aldicarb, carbaryl, oxamyl, methomyl, pirmicarb, and thiodicarb. At present time the

only RBC and whole brain ChE data for formetanate HCl, methiocarb, and propoxur are from EPA's NHEERL dose-response and time course studies in male rats. For carbofuran, a total of two studies are available, one providing RBC and whole brain ChE inhibition data and one study providing only RBC data; with all of the carbofuran data for male rats only.

For those chemicals which have data in male and female rats, EPA analyzed both sexes. When male and female data provided statistically similar BMD_{10}s, the data were combined and analyzed jointly. This joint analysis provides a more robust analysis using all the available data. In cases where the BMD estimates were statistically different, sex specific BMD_{10}s are presented (Tables I.B.3, 5, 6). As mentioned above, only male data are available for four NMCs. Regarding RBC ChE inhibition from pirimicarb, reliable BMD_{10} estimates could not be calculated due to a lack of response even at the highest doses tested (110 mg/kg).

ChE inhibition measured using both radiometric and modified Ellman techniques are available for aldicarb (MRID Nos. 45068601, 45150701, MRID pending), carbaryl, methomyl, and oxamyl. RBC and brain ChE data from the two methods provided statistically similar BMD_{10} estimates for aldicarb, methomyl, and oxamyl and were thus combined in the analysis to provide a more robust potency estimate. As shown in Table I.B.3, for carbaryl, both methods provided similar BMD_{10} estimates for RBC ChE. However, for brain ChE, the BMD_{10} estimated from EPA's radiometric study is larger than that estimated from the registration studies (i.e., modified Ellman). Four registration studies were included in the analysis (MRID nos. 43845202, 43845203, 44122601, 44393701). For all four studies, Sprague-Dawley rats were administered via gavage with an aqueous vehicle of 0.5% (w/v) carboxymethyl-cellulose (high viscosity)/0.1% (w/v) Tween 80 (10mL/kg). EPA's experiments involved Long Evans rats dosed via gavage with corn oil (1 mL/kg) as the administration vehicle. Given that each of the carbaryl studies provide valid and acceptable ChE data, there is no scientific support for removing any studies from the analysis. Thus, the Agency has decided to include all the available brain ChE data in the carbaryl BMD_{10} estimate used for potency determination.

Table I.B.3. Oral BMD_{10}s and $BMDL_{10}$s from rat brain and RBC ChE inhibition for the *N*-methyl carbamates[1].

Chemical	Brain		RBC	
	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)	BMD_{10} (mg/kg)	$BMDL_{10}$ (mg/kg)
Aldicarb	F= 0.05 M= 0.06	F= 0.03 M= 0.03	0.03	0.02
Carbaryl	Registration F= 1.60 Registration M= 1.21 NHEERL M=5.46 Combined M=1.58	Registration F= 1.35 Registration M= 0.99 NHEERL M= 4.15 Combined M= 1.11	5.59	3.41
Carbofuran[2]	0.15	0.13	0.03	0.01
Fermetanate HCl[2]	0.10	0.05	0.09	0.03
Methiocarb[2]	1.31	0.56	3.18	0.81
Methomyl	0.49	0.33	0.34	0.26
Oxamyl	F= 0.14 M= 0.18	F= 0.11 M= 0.14	0.28	0.16
Pirimicarb	11.96	6.98	NA	NA
Propoxur[2]	2.09	0.83	1.54	0.28
Thiodicarb	0.27	0.23	1.39	0.90

1. BMD estimates are presented as a single estimate when there are no differences between sexes and between the radiometric and modified Ellman methods, unless otherwise noted.
2 BMD estimates are for male only
NA: No relationship between RBC ChE activity and pirimicarb dose.

Figure I.B.1. Plot of BMD_{10}s and the 95% confidence limits for rat brain ChE inhibition for the *N*-methyl carbamates

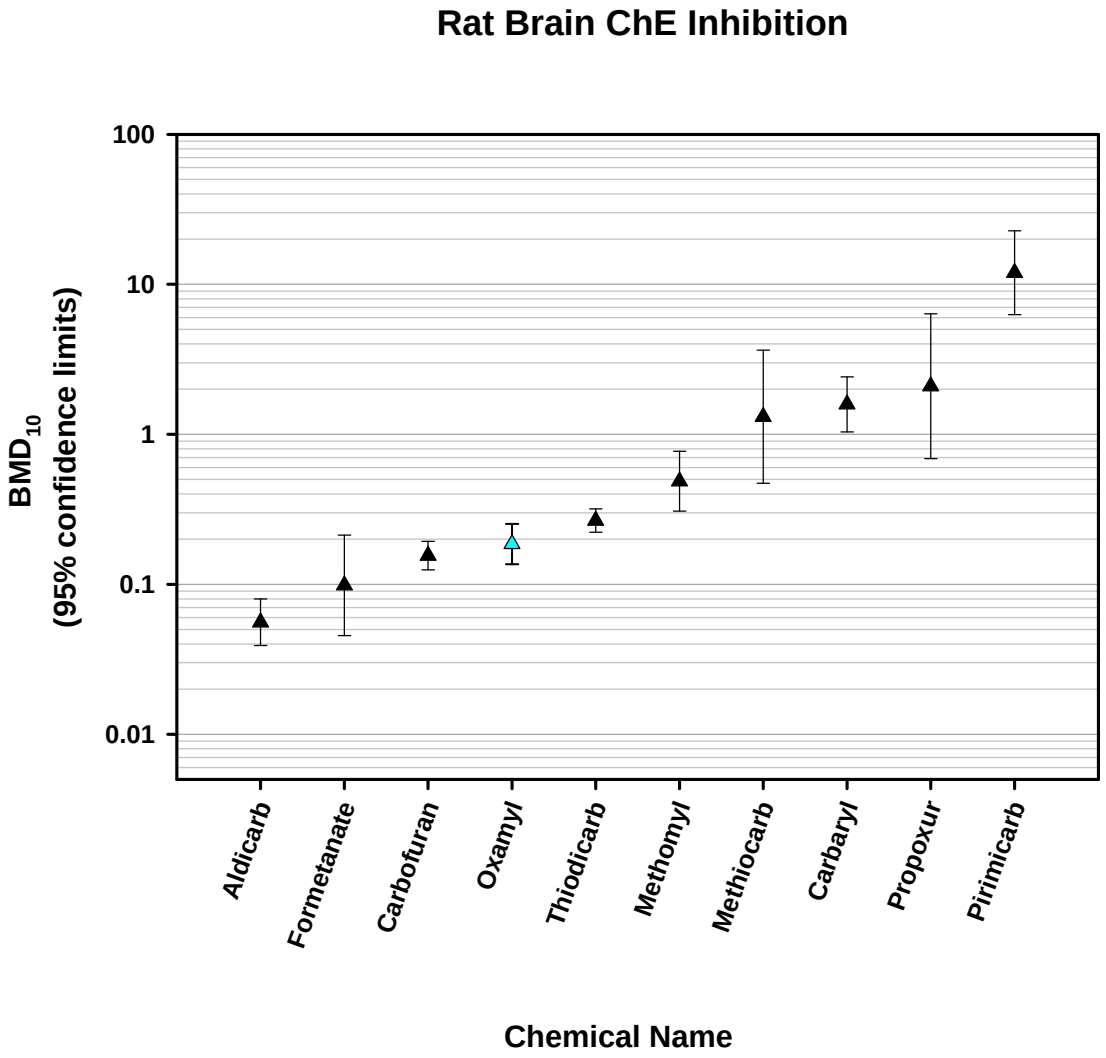
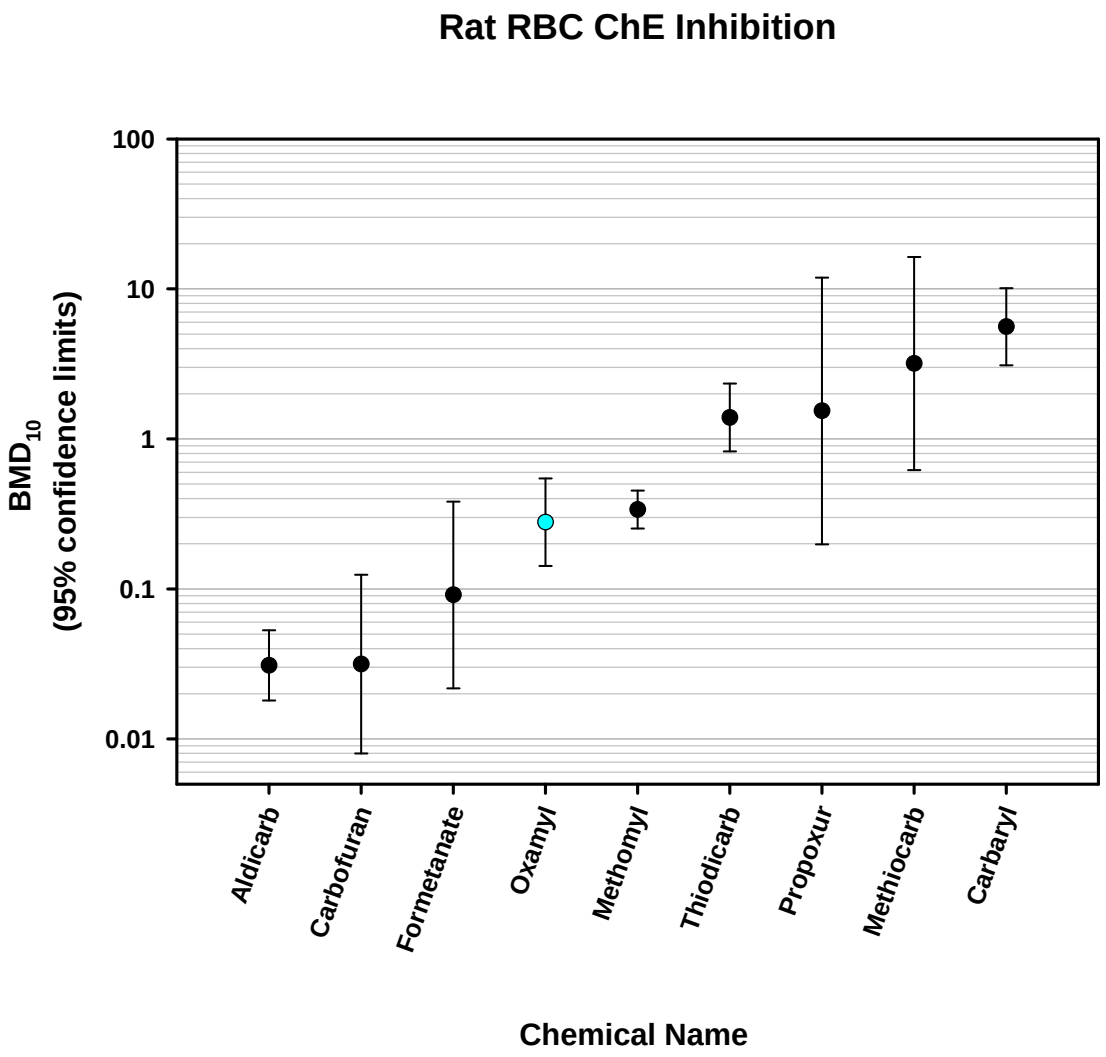


Figure I.B.2. Plot of BMD_{10}s and the 95% confidence limits for rat RBC ChE inhibition for the *N*-methyl carbamates



BMD_{10}/ $BMDL_{10}$ for RBC ChE were not developed for pirmicarb; no dose-response relationship was observed up to highest dose tested (110 mg/kg).

Potency estimates used for calculating dermal and inhalation RPFs are provided in Table I.B.4 and I.B.5. Dermal and inhalation RPFs are needed because carbaryl, methiocarb, and propoxur have residential uses. Sufficient dose-response data were available for carbaryl to calculate BMD_{10} estimates for RBC and brain ChE via the dermal route. However in the dermal studies with methiocarb and propoxur, no ChE inhibition was observed up to the highest doses tested. The highest doses in the methiocarb and propoxur studies have been used to estimate dermal relative potency.

Rat inhalation data with propoxur were available to estimate a BMD10 for brain ChE. Inhalation studies with carbaryl and methiocarb are not available. Route specific studies are preferred since they account for route specific kinetic characteristics which may impact chemical potency. In the absence of inhalation studies, oral data are being used in the preliminary cumulative risk assessment to estimate inhalation relative potency for carbaryl and methiocarb. This introduces uncertainty regarding the estimation of cumulative risk for the inhalation pathway. However, given that these chemicals do not have a port of entry effect, are expected to be rapidly absorbed, and do not require activation, ChE measured from oral studies are not expected to substantially underestimate potency. (Note: Data from dermal and inhalation studies with oxamyl are not provided here because oxamyl does not have residential uses. See Section I.B.5 for Selection of Index Chemical [Oxamyl])

Table I.B.4. Dermal BMD_{10}s, $BMDL_{10}$s, and potency estimates from rat and rabbit brain and RBC ChE inhibition for the *N*-methyl carbamates with residential/non-occupational uses

Chemical	Brain		RBC	
	BMD_{10} (mg/kg)	**$BMDL_{10}$ (mg/kg)**	**BMD_{10} (mg/kg)**	**$BMDL_{10}$ (mg/kg)**
Carbaryl[2]	49.35	30.56	F= 86.18 M= 59.04	F= 60.55 M= 46.91
Methiocarb[3]	375[1]			
Propoxur[3]	1000[1]			

1, Dermal endpoint is based on the highest dose tested in the dermal study; No ChE inhibition was observed at any dose.
2. Data from rat studies
3. Data from rabbit studies
4. See Table I.B.7 for brain BMD10s and BMDL10s for oxamyl

Table I.B.5. Inhalation BMD_{10}s, $BMDL_{10}$s, and potency estimates from rat brain and RBC ChE inhibition for the *N*-methyl carbamates with residential/non-occupational uses.

Chemical	Brain		RBC	
	BMD_{10}	$BMDL_{10}$	BMD_{10}	$BMDL_{10}$
Carbaryl[1]	1.58 mg/kg	1.11 mg/kg	5.59 mg/kg	3.41 mg/kg
Methiocarb[1]	1.31 mg/kg	0.56 mg/kg	3.18 mg/kg	0.81 mg/kg
Propoxur[2]	F= 0.0095 mg/L M= 0.016 mg/L (converted to 4.54 mg/kg for RPF calculation)	F= 0.0076 mg/L M= 0.011 mg/L	NA	NA

[1] No inhalation studies are available for carbaryl and methiocarb; potency estimates are from oral studies
[2]Inhalation BMDs and BMDLs for propoxur were different between sexes, therefore are displayed separately. No apparent dose-response for RBC inhalation for propoxur and therefore no BMD.

c. Results: Half Life Time to Recovery (This section still needs work)

Half lives for time to recovery from oral studies are provided in Table I.B.6. For most of the NMCs, recovery half life estimates for brain and RBC AChE inhibition range from <1 hour up to 6 hours. Recovery half lives increased with dose for brain and RBC AChE in carbaryl studies. A similar trend was noted for RBC AChE from female rats exposed to aldicarb and male rats exposed to carbofuran. With the exception of RBC AChE inhibition following aldicarb exposure, no sex differences were noted in recovery half lives.

At higher doses of carbaryl, recovery half-life for oral exposure was estimated to approximately 12 hours. However, at lower doses more relevant for risk assessment purposes, the half-life for carbaryl cholinesterase inhibition was estimated to 6-8 hours and shorter.

Regarding thiodicarb, the available cholinesterase data were not sufficiently robust to estimate brain cholinesterase half-life. Furthermore, the RBC cholinesterase data provide an estimate of recovery half-life of 13 hours with wide upper/lower confidence limits of 6 and 28 hours. As described in II.B.2, overall, the RBC cholinesterase data for thiodicarb are highly variable. Thus, the half-life estimates provided in Table I.B.6 for thiodicarb may not be reliable.

Overall, the half-life to recovery data support the use of acute, single day exposures in the NMC cumulative risk assessment.

Table I.B.6. Half life for time to recovery from oral rat studies for brain and RBC ChE inhibition for the *N*-methyl carbamates.

Chemical	Brain		RBC	
	Recovery Half-Life Estimate (hrs)	Upper & Lower Confident Intervals (hrs)	Recovery Half-Life Estimate (hrs)	Upper & Lower Confident Intervals (hrs)
Aldicarb	1.52	1.16-1.99	F (-inf, 0.1) 1.10 (0.1.0.3) 2.91 (0.3,0.5) 3.39 (0.5, Inf) 5.90 M (-inf,0.1) 1.91 (0.1,0.3) 1.20 (0.3,0.5) 1.62 (0.5, Inf) 1.50	F 0.50-2.40 1.96-4.33 2.35-4.90 3.52-9.91 M 1.31-2.79 0.87-1.64 1.19-2.21 0.80-2.82
Carbaryl	(0,10) 1.83 (10,50) 4.08 (50,125) 12.45	1.23-2.72 3.43-4.85 10.67-14.53	(0,10) 6.64 (10,50) 8.76 (50,125) 11.35	1.91-23.08 5.36-14.31 7.85-16.41
Carbofuran[1]	2.49	0.81-7.70	(0,0.5) 1.60 (0.5,1.5) 3.08	1.13-2.29 2.36-4.01
Formetanate[1]	4.05	3.02-5.44	4.86	3.03-7.81
Methiocarb[1]	2.77	1.91-4.01	5.40	2.55-11.43
Methomyl	0.80	0.70-0.93	0.61	0.39-0.95
Oxamyl	0.75	0.66-0.86	0.81	0.66-0.10
Pirimicarb	NA	NA	NA	NA
Propoxur[1]	2.69	1.02-7.04	0.55	0.32-0.93
Thiodicarb	NA	NA	12.84	5.92-27.85

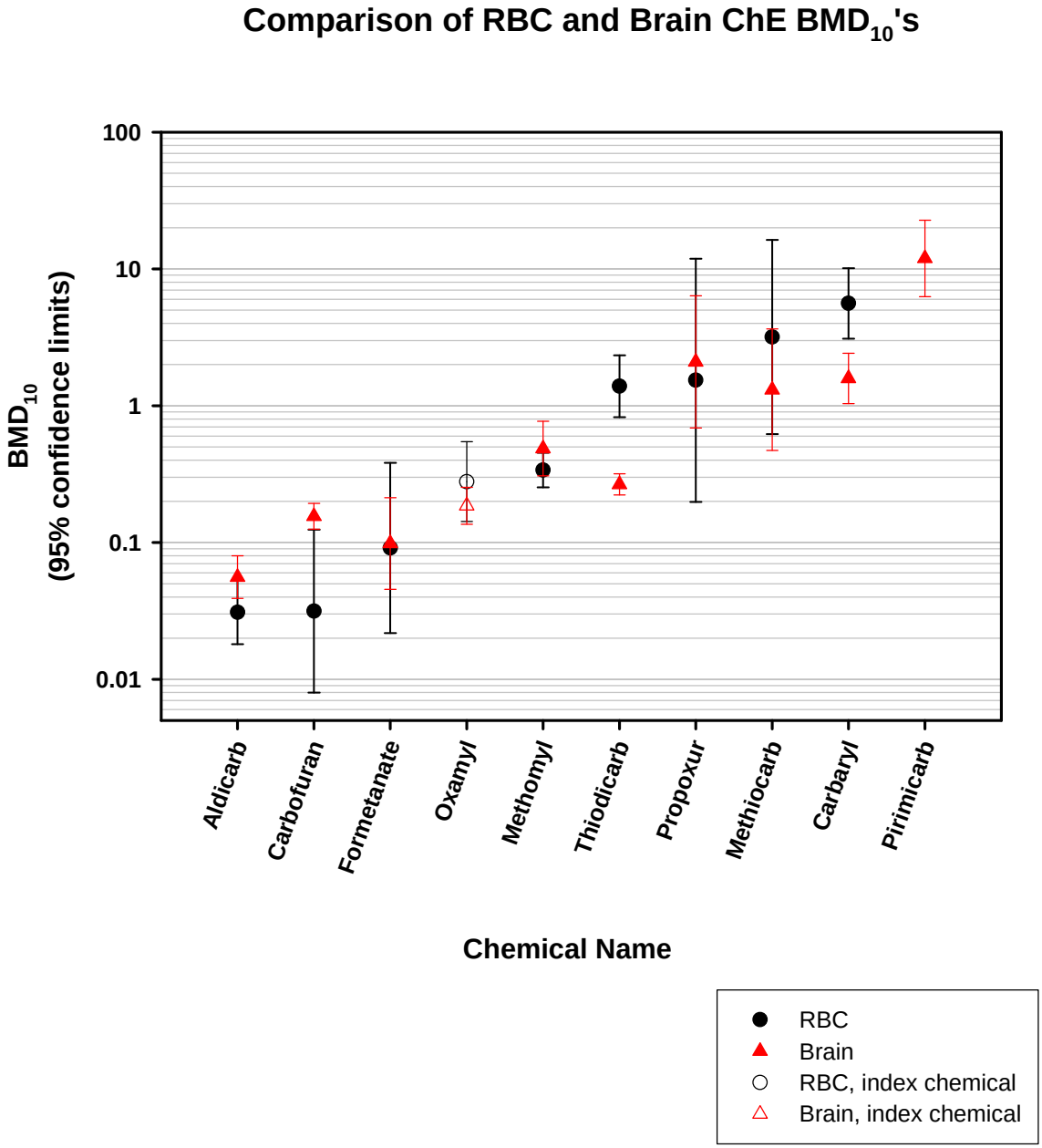
1. BMD estimates are for male only

4. Selection of Relative Potency Factors: Brain ChE Inhibition

A key component of cumulative hazard assessment is to select an endpoint pertinent to the common mechanism of toxicity that can be used to quantify cumulative risk. EPA is proposing to quantify cumulative risk to the NMCs using RPFs and PoDs from brain ChE data. As mentioned above, in cases where male and female rats provide similar BMD_{10} estimates, EPA has developed potency estimates jointly (methomyl, pirimicarb, thiodicarb). At the present time, only male data are available for carbofuran, formetanate HCl, methiocarb, and propoxur. For NMCs where the female and male data provided statistically different results (aldicarb, carbaryl, oxamyl), the male BMD_{10} has been used to calculate relative potency and PoDs.

As shown in Figure I.B.3, BMD_{10} estimates of brain ChE inhibition are generally similar to those for RBC ChE data. For the five most potent NMCs, brain ChE is equally sensitive or more sensitive compared to RBC ChE inhibition. Thus, brain ChE inhibition data provide a health protective endpoint for estimating cumulative risk on both the central and peripheral nervous system. Compared to BMD_{10} estimates based on RBC ChE, BMD_{10} estimates based on brain ChE have tighter confidence intervals and therefore will confer less uncertainty on cumulative risk estimates. Moreover, brain ChE inhibition represents a direct measure of the common mechanism of toxicity as opposed to using surrogate measures (e.g., blood measures).

Figure I.B.3. Comparison of BMD_{10}s and the 95% confidence limits for rat brain and RBC ChE inhibition for the *N*-methyl carbamates.



5. Selection of the Index Chemical (Oxamyl)

The cumulative risk assessment guidance document (USEPA, 2002a) states that the index chemical should be selected based on the availability of high quality dose-response data, preferably in each route of interest, for the common mechanism endpoint and that it acts toxicologically similar to other members of the common mechanism group. High quality dose-response data allows the calculation of PoDs for oral, dermal, and inhalation exposures with confidence. Because the PoD for the index chemical is used to extrapolate risk to the exposure levels anticipated in the human population, any error or uncertainty in an index chemical's PoD value will be carried forward in the cumulative risk estimates.

a. Candidates for the Index Chemical

When selecting the index chemical, EPA evaluated the availability of quality oral, dermal, and inhalation studies for all ten NMCs. Dermal toxicity studies that provided RBC and whole brain data were available for 4/10 NMCs (carbaryl, methiocarb, oxamyl, propoxur). Inhalation studies were available for only propoxur and oxamyl.

At present time, the only NMCs with studies in all three routes of interest are oxamyl and propoxur. As shown in Table I.B.2, the oxamyl database of oral studies is more robust than propoxur. Moreover, the oxamyl dermal study in rabbits provides more robust dose-response data compared to the propoxur rabbit dermal study (Tables I.B.4 and I.B.7). Oxamyl has been selected as the index chemical for Preliminary Cumulative Risk Assessment of the NMCs.

b. Description of the Oxamyl Database

Oxamyl has robust oral database. Three acute oral registration studies are available. Radiometric ChE data are available from EPA's NHEERL dose-response and time course studies. Doses in oral studies ranged from 0.005 mg/kg to 15.3 mg/kg and thus provide a broad dose-response range. RBC ChE was measured at the time of peak effect in three datasets. Whole (or half) brain ChE data are available from four studies. High quality recovery data are also available. As shown in Table I.B.3, the brain BMD_{10}s for male and female rats were statistically different (0.18 and 0.14 mg/kg, respectively). Although statistically different, given the wide range of potencies shown by the NMCs, the male and female BMD_{10}s are remarkably similar. For both sexes, the confidence limits on the BMD_{10}s are narrow. Thus the $BMDL_{10}$s provide robust values for the extrapolating cumulative risk.

Two dermal studies were available for oxamyl, both in the rabbit. Oxamyl exhibited a good dose-response relationship for assessing cholinesterase activity with RBC and brain. The effect of sex on dose was not significant in either study or compartment. RBC and brain (half-brain) ChE activities for both studies were measured once, at the end of the study. The dermal brain and RBC ChE BMD_{10}s are 34.91 mg/kg and 64.01 mg/kg, respectively.

An acute (single day, 4 hours) inhalation toxicology study (MRID 45155801) is available for oxamyl. Brain and RBC ChE inhibition were measured at the end of the study. The BMD analyses indicate a good dose-response relationship for assessing ChE activity with RBC and brain. ChE inhibition was similar for both RBC and brain compartments in both sexes. The inhalation brain and RBC ChE BMD_{10}s are 0.0004 mg/L and 0.002 mg/L, respectively.

A detailed description of the benchmark dose analysis for dermal and inhalation studies in oxamyl can be found in Appendix II.B.2. Table I.B.7 provides the brain BMD_{10}s and $BMDL_{10}$s for oxamyl.

- ❑ Oxamyl brain **BMD_{10}s** for oral, dermal, and inhalation routes have been used to calculate the oral, dermal, and inhalation *RPFs* for the preliminary cumulative risk assessment.

- ❑ Oxamyl brain **$BMDL_{10}$s** for oral, dermal, and inhalation routes have been used as the oral, dermal, and inhalation *PoDs* in the preliminary cumulative risk assessment.

Table I.B.7. Oral, dermal, and inhalation brain BMD_{10}s and $BMDL_{10}$s for OXAMYL, the index chemical.

Endpoint	Oral	Dermal	Inhalation
BMD_{10}	0.18 mg/kg	34.91 mg/kg	0.00040 mg/L (converted to 0.083 mg/kg)
$BMDL_{10}$	0.14 mg/kg	17.05 mg/kg	0.00024 mg/L (converted to 0.050 mg/kg)

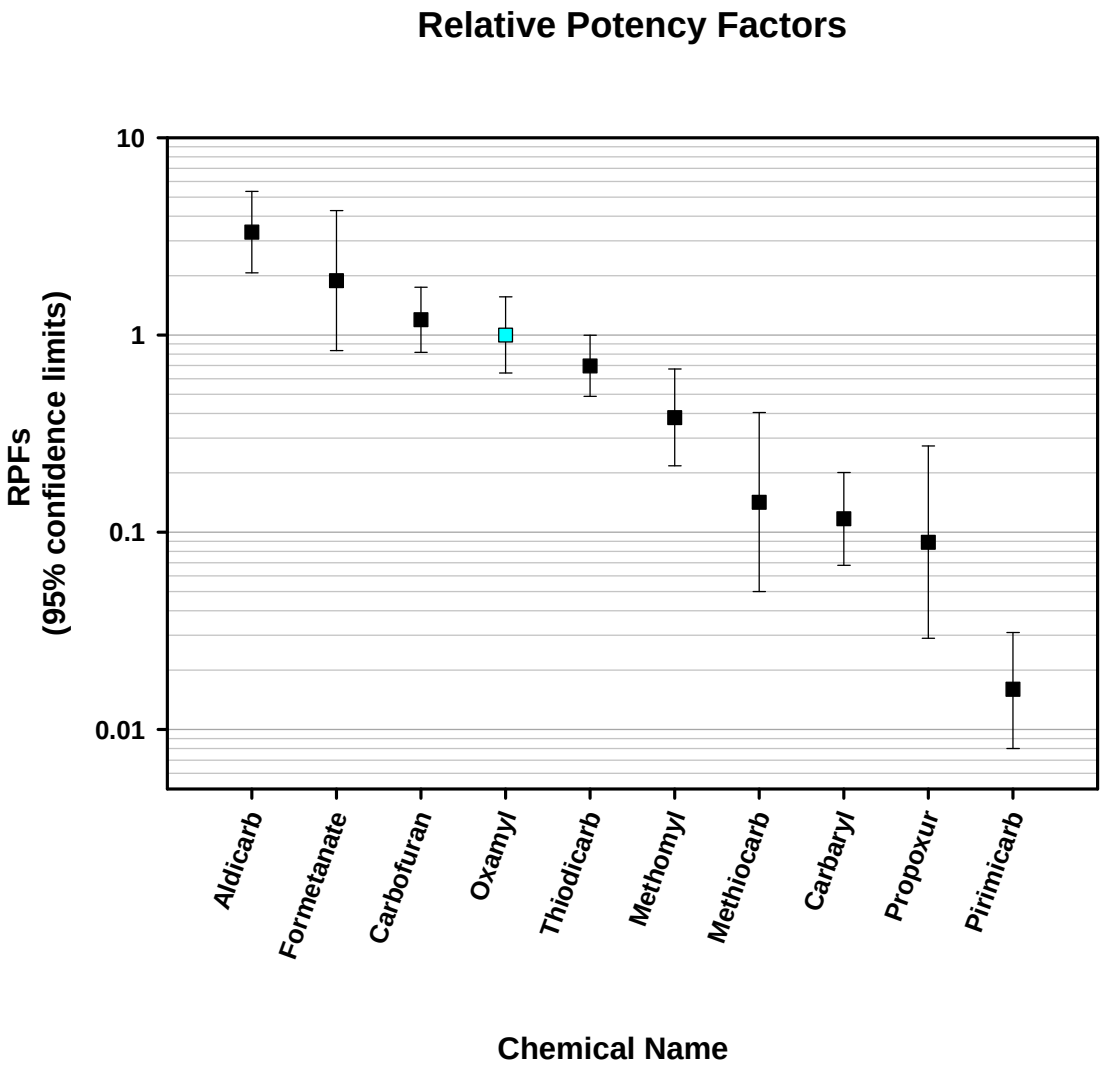
6. Relative Potency Factors for the Preliminary Cumulative Risk Assessment of the *N*-Methyl Carbamates

RPFs were calculated from endpoints for brain ChE inhibition provided in Tables I.B.3, 4, 5, and 7. An RPF is the ratio of the BMD_{10} of oxamyl divided by the BMD_{10} (or appropriate value) for each NMC. RPFs are listed in Table I.B.8. Oral RPFs and the respective 95% confidence limits are shown graphically on Figure I.B.4.

Table I.B.8. Relative Potency Factors for Oral, Dermal, and Inhalation routes.

Chemical	Oral RPF	Dermal RPF	Inhalation RPF
Aldicarb	3.32		
Carbaryl	0.12	0.71	0.05
Carbofuran	1.19		
Fermetanate	1.89		
Methiocarb	0.14	0.09	0.06
Methomyl	0.38		
Oxamyl	1.00	1.00	1.00
Pirimicarb	0.02		
Propoxur	0.09	0.03	0.02
Thiodicarb	0.70		

Figure I.B.4. Plot of oral relative potency factors for rat brain ChE inhibition for the *N*-methyl carbamates.



7. Uncertainty, Extrapolation, and FQPA 10X Factors

Typically EPA applies uncertainty and extrapolation factors to account for interspecies and intraspecies variability and potential database uncertainty. The FQPA also mandates that a 10X factor be applied to protect for infants and children unless there is sufficient data to support removal of the 10X. At present time, EPA has not determined the appropriate uncertainty or extrapolation factors, including the interspecies and the FQPA 10X factors, for the NMC cumulative risk assessment.

The rat provides the basis for the RPFs and PoDs in the preliminary cumulative risk assessment for the NMCs. As such, a consideration of interspecies extrapolation is necessary. EPA typically applies a 10X factor to account for differences in animals and humans. Oral studies with adult, human subjects and measuring blood ChE inhibition are available for aldicarb, carbofuran, methomyl, oxamyl, and propoxur. There are also some pharmacokinetic data from a biomonitoring study with carbaryl. A meeting of the FIFRA SAP is expected to evaluate ethical and scientific considerations for the use of human intentional dosing studies. Cumulative risk assessment issues regarding interspecies extrapolation are expected to be covered during this SAP meeting. The Agency will consider the comments from the panel and public prior to determining the appropriate chemical specific interspecies factors. The revised cumulative risk assessment of the NMCs is expected in winter 2006. The Agency expects to determine the chemical specific interspecies factors in its revised cumulative risk assessment.

In June, 2002, the FIFRA SAP provided the Agency comments regarding the evaluation of sensitivity of infants and children as part of the peer review of the revised OP cumulative risk assessment (FIFRA SAP, 2002). The Agency believes that many of the comments provided by the panel at that time also apply to the NMC common mechanism group. The Agency provided the NMC pesticide registrants a letter notifying the Agency's intentions regarding application of the FQPA 10X factor for this common mechanism group (Edwards, 2004). That letter states that

> *"Given that age-related sensitivity has been shown for other chemicals which inhibit acetylcholinesterase and that at present time there is limited acetylcholinesterase inhibition data on juvenile or young animals following exposure to the N-methyl carbamates, there is uncertainty regarding age-dependent sensitivity following exposure to the N-methyl carbamates. Thus, in the absence of information to the contrary, an FQPA safety factor may be appropriate in the cumulative risk assessment for the N-methyl carbamate pesticides."*

For each individual NMC, the magnitude of the FQPA 10X factor will be based in large part on 1) ChE dose response data comparing relative sensitivity of adult and juvenile animals and 2) ChE recovery data comparing recovery times in adult and juvenile animals. The Agency anticipates the submission of

comparative sensitivity studies for some chemicals in the coming months. New studies which become available by October 1, 2005 will be incorporated in the revised cumulative risk assessment for the NMCs.

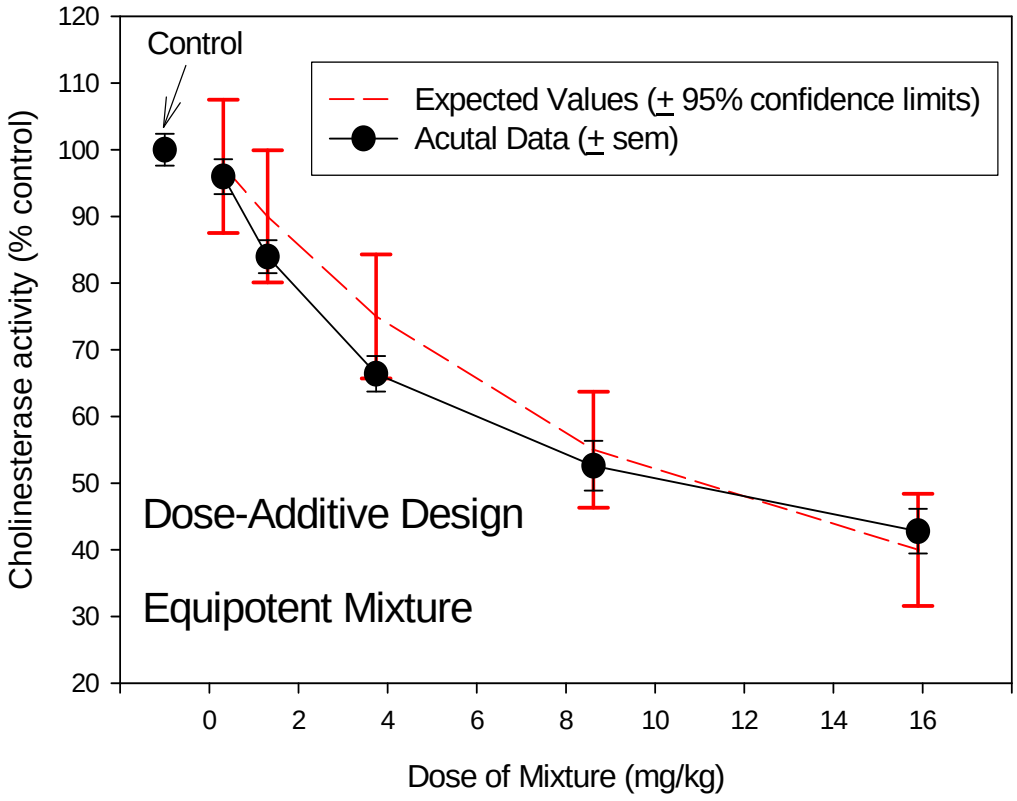
8. On-going Research Efforts to Support the NMC Cumulative Risk Assessment

Relative potency and time to recovery are important aspects of cumulative hazard assessment for the *N*-methyl carbamates pesticides. Ideally, a PBPK model could be used to account for chemical specific characteristics of ChE inhibition and recovery. However, the data to support such a model do not exist at present time and are not likely become available prior to the tolerance reassessment deadline of August, 2006 mandated under the FQPA. EPA does, however, acknowledge the importance of improving cumulative risk assessment methodologies. To that end, EPA's National Exposure Research Laboratory (NERL) has developed a PBPK/PD model for carbaryl and has begun a research effort to model multiple pesticides (Powers et al, 2005). The status of these models is summarized in Appendix II.B.6. NHEERL scientists are investigating tissue dose and pharmacokinetics of carbaryl and are investigating ChE reactivation *in vitro.* These modeling and laboratory efforts may not impact the quantitation of cumulative risk to the NMCs but aid in the characterization of risk for this group. Furthermore, the lessons learned during the development of these models will aid the Agency in future cumulative risk assessments.

In the absence of a PBPK/PD model, the Agency is relying on the RPF method. A key assumption of the RPF method is dose additivity. While there are a few interaction studies of *N*-methyl carbamate and OP pesticides in the literature (e.g., Gupta and Dettbarn, 1993; Takahashi et al., 1987), no studies conducted using mixtures of more than two *N*-methyl carbamates and which use lower dose levels (i.e., that do not produce lethality or profound toxicity) have been identified.

NHEERL scientists have conducted a mixture study using seven *N*-methyl carbamates (carbaryl, carbofuran, formetanate, methiocarb, methomyl, oxamyl, and propoxur). In the mixture study a dose-additive experimental design was used and the proportion of the carbamates in the mixture was based on their potency using the individual-chemical benchmark dose values as the point of comparison. Five different dosage levels of the mixture were given, predicted to produce <5%, 10%, 25%, 45% or 60% brain ChE inhibition. Each NMC was given alone at a previously tested dosage to confirm the original dose-response data (7 single-chemical experimental groups). The degree of cholinergic toxicity, motor activity, and RBC and brain ChE were measured. As can be seen from Figure I.B.5 below, increasing dosages of the mixture produced increasing decrements in brain ChE activity. Moreover, the dose-additive model predicted the degree of ChE inhibition within the 95% confidence limits of each predicted value. Analysis of the RBC ChE and motor activity data from the mixture study have not been completed.

Figure I.B.5. Plot of brain ChE measured in a seven chemical mixture of *N*-methyl carbamates.



9. Summary

The Hazard Characterization for the Preliminary Cumulative Risk Assessment of the NMCs is contained in Section I.H.

This chapter has described the application of the RPF method in the preliminary cumulative hazard assessment for the NMCs. Whole brain ChE is a sensitive, health protective endpoint representing the target tissue. The brain data provide the most appropriate dataset for extrapolating cumulative risk to this common mechanism group. Potency for the NMCs varies over several orders of magnitude. Analysis of recovery ChE recovery data suggests that half-life time to recovery ranges from a few minutes up to 13 hours, is chemical dependant and for some chemicals is dose dependant. Overall, the analysis of recovery data supports the Agency's assumption that at the low concentrations found in the environment the appropriate duration of exposure for the NMC cumulative risk assessment is acute exposure. Oxamyl has been selected as the index chemical. BMD_{10} estimates of brain ChE from oral, dermal, and inhalation studies were used to develop RPFs for the NMCs. $BMDL_{10}$ estimates of brain ChE from oral, dermal, and inhalation studies represent the PoDs for the NMCs cumulative risk assessment. EPA has not yet determined the appropriate uncertainty and extrapolation factors.

C. Cumulative Risk From Pesticides in Foods

The exposure assumptions for these assessments, which are described in the following discussion, are similar to those that were used for the OP CRA.

1. Method of Estimation of Cumulative Dietary Risk

Dietary exposure was estimated using the Dietary Exposure Evaluation Model software and incorporating the Food Commodity Intake Database (DEEM-FCID™). A joint distributional analysis was conducted by combining representative data on concentrations of 10 N-methyl carbamate pesticides on foods with distributions of anticipated consumption of these foods by different segments of the U.S. population. The primary advantage of a joint distribution analysis is that the results are in the form of a simultaneous analysis (i.e., a distribution) of exposures that demonstrate both realistic best-case and realistic worst-case scenarios of exposure.

2. Selection of Oral Relative Potency Factors

Ten chemicals were included in this N-methyl carbamate cumulative assessment group. A list of the chemicals and their RPFs is presented in Table I.C.1. These chemicals were selected based on their inclusion in the CAG as described in Federal Register Notice FRL–7334–4 February 4, 2004 “Carbamate Cumulative Assessment Group; Availability” (USEPA, 2004) and their occurrence in the PDP monitoring data collected between the years 1994 and 2002. Exposure estimates provided in Section VII of this document are RPF-adjusted (i.e., expressed in mg/kg of index –chemical equivalents). The index chemical is Oxamyl.

3. Dietary (Food) Residue Input Data for Dietary Risk Assessment

Anticipated concentrations of N-methyl carbamates in foods were based on residue monitoring data collected by the PDP. These data are available for downloading from the PDP internet site (http://www.ams.usda.gov/science/pdp/). For this preliminary assessment we used data collected from 1994 through 2003. The selection of commodities and chemicals analyzed by PDP varies from one year to the next but most of the N-methyl carbamate pesticides of concern were analyzed throughout this period. In particular, PDP survey data for the period includes high consumption foods for children.. Residues (if any) from fish and eggs were not included in this assessment but are not anticipated to contribute to risk from carbamate pesticides.

The analyses of N-methyl carbamates by PDP are summarized on their web site. The 65 food forms in the PDP data with analytical data between 1994 and 2003 were used as the source of residue data for their matching food forms in the DEEM-FCID software (CSFII consumption data). Food processing factors

were applied to specific chemical/commodity pairs to extend these data for use on cooked and processed food/food forms in the analysis. Table II.C.1-1 in Appendix II.C.1 shows the food forms of commodities monitored by PDP included in the food exposure assessment along with chemical specific processing factors to translate these residue values to food forms not included in PDP. The factors are intended to adjust residues in foods for changes that can occur in food preparation procedures such as cooking, canning, curing, and drying. Processing factors are based on the submitted processing studies, published data, or logical calculations in the absence of submitted studies (e.g., estimates based on loss of water in drying fruits). The absence of a processing factor in Table II.C.1-1 in Appendix II.C.1 indicates that either no residues were detected in that chemical/food form combination or there is no registered use for that chemical/food form combination.

As was done with the OP pesticides in the OP CRA, the PDP residue data were further extended to other commodities identified as reasonable for translation of pesticide residue data per OPP/HED SOP 99.3 (USEPA, 1999b); see Table II.C.1-1 in Appendix II.C.1.

4. Manipulation of Residue Data for Exposure Assessment

Commonly, the following equation is used for estimating exposure by the food pathway for a single chemical:

$$\text{Exposure} = \text{Residue} \times \text{Consumption}$$

In the case of cumulative exposure assessment, the residue term in the first equation is changed to Index Equivalent Residue.

The calculated cumulative residue is a simple arithmetic addition of residues of different chemicals that have different toxicities (potency) and therefore simple addition of their residues is not appropriate. For that reason, the amount of residue of each chemical is adjusted by multiplying by a ***Relative Potency Factor (RPF)*** to get the equivalent residue of an index chemical. This new calculated residue is termed ***Index Equivalent Residue (Residue$_{IE}$)*** and the exposure value resulting from combining Residue_{IE} and consumption is termed ***Index Equivalent Exposure (Exposure$_{IE}$)***. The new central equation for exposure will then become:

$$\text{Exposure}_{IE} = \text{Residue}_{IE} \times \text{Consumption}$$

The following discussion explains in more detail how this was accomplished for this case study.

a. Generation of Cumulative Equivalent Residue (Residue$_{IE}$)

To determine a given one-day cumulative oral exposure to multiple N-methyl carbamate chemicals, first an Index Equivalent Residue (Residue$_{IE}$) for each residue value is calculated. On a given PDP sample, each residue value is multiplied by any applicable processing factor (PF) for that chemical on the food sample of interest and the Relative Potency Factor (RPF) for the same chemical to express it as an Residue$_{IE}$ for that chemical; this is step 1.

Step 1: **Residue$_{IE}$ (per chemical n) = Residue X PF$_n$ X RPF$_n$**

The cumulative Residue$_{IE}$ for all chemicals detected on one PDP sample will then be the sum of all the Residue$_{IE}$ for all the chemicals on that sample; this is step 2.

Step 2: **Cumulative Residue$_{IE}$ = $\sum$ Residue$_{IE}$** (per PDP sample)

For example, given 100 samples of apples and 10 N-methyl carbamates, there will be generated 10 Residue$_{IE}$ values for each sample; hence a total of 100 * 10 = 1000 Residue$_{IE}$ values from step 1. In step 2, each set of 10 Residue$_{IE}$ for a sample is summed to generate a cumulative Residue$_{IE}$ per one sample; hence 100 cumulative Residue$_{IE}$ points for 100 samples of apples are generated.

By summing on a sample-by-sample basis, the potential for capturing any co-occurrence on the same commodity is enhanced. Another very important advantage of this approach is that, using appropriate record keeping (see next section), the complete history of each cumulative residue value in the exposure assessment can be potentially traced back to its origins. All of the sample collection and analytical information associated with a given PDP sample and all arithmetic adjustments incorporated in producing a Residue$_{IE}$ can be traced in the process of sensitivity analysis or critical food commodity contribution analysis.

i. N-methyl Carbamate Food Residue Database

The data manipulations necessary to prepare the PDP residue data for input into the risk equation are in principle very simple; however, the task of performing these calculations for multiple chemicals and food commodities is problematic. The residue data used in this case study consist of over 583,000 records of analytical data and sample information. The processing factors account for several thousand additional records of information. For this reason, and in anticipation of the need to make multiple uses of the data, to keep track of them, and work backward from the cumulative assessment results to determine contributors, all the data manipulation were conducted using relational database techniques. The N-methyl Carbamate food residue database is based on the same design as the one used for the OP Cumulative Risk Assessment. The database consists of, among other things, four major data tables:

1 Residue data table: contains essentially all of PDP sample and analyses data for N-methyl carbamate pesticides for the years 1994-2003.

2 Processing factor data table: containing all relevant processing factors for specific food form/chemical combinations. (Table II.C.1-1 in Appendix II.C.1 is extracted from these data).

3 RPF Table: containing the relative potency factors for all chemicals of interest.

4 Translation Table: providing bridging links between PDP commodity codes, such as *AP*, and all corresponding DEEM-FCID food forms, such as *Apple, fruit with peel; Uncooked; Fresh or N/S; Cook Meth N/S*. This table allows the assignments of translation of data between PDP commodities also, such as cantaloupe data to watermelon food forms

These four tables are linked through common fields, including pesticide codes and commodity codes. Calculation queries are coded into the database so that all the pertinent PDP samples records can be extracted, each calculation outlined above can be performed, and the results can be sorted and output in various formats for further analysis.

A cumulative residue calculation query performs the two-step process described earlier, extracting the various parameters needed from the four tables described above. The calculation is

performed on all of the food samples that are of interest and the results are compiled in text files containing the cumulative distributions for each food commodity of interest.

Each text file contains a header with sample information (number of values, number of detects, number of zeros, average of residues) and all of the cumulative residue values for a single food form, sorted in descending order.

By maintaining all of the calculation inputs in separate tables in the database, it is possible to repeat the above process with new inputs by simply replacing or adding data to the appropriate table. For example a specific chemical can be omitted from the entire process by assigning it a value of zero in the RPF table. Specific chemical/commodity combinations can be selectively omitted by entering a zero value for that pair in the processing factor table.

ii. Generation of Exposures

The cumulative $Residue_{IE}$ values (text files described in the previous section) are treated as distributions of representative residues and linked to all appropriate food forms; cumulative residue values are then randomly picked and combined with a consumption record to generate a single exposure value which is termed $Exposure_{IE}$. This process (Monte Carlo in nature and conducted by DEEM-FCID software) is repeated many times per each consumption record to generate a distribution of exposure values. This process has been described in public documents and proceedings of the FIFRA Scientific Advisory Panel (*FIFRA SAP, 2000a*).

iii. Assumptions

The assumptions in this cumulative assessment case study, which are summarized below, are essentially identical to those used for the OP Cumulative Risk Assessment.

The input residue data were drawn from the PDP data base. The PDP program tests different commodities for various pesticides in 10 states throughout U.S. The residue data of 1994 to 2003 were used in this assessment. The following assumptions were made in the process:

1) Although PDP has started single-unit sampling for limited crops (apples and pears) since 1998, only the residue data from composite samples were utilized in this assessment for the sake of simplicity. A single composite sample may contain several individual serving of some foods; it is

implicitly assumed that all these single servings in a composite sample have residues no more or less than the composite residue (average value). For purposes of the present example, it is assumed that residues reported on composite homogenates adequately reflect the residues in any given single serving contained in that homogenate. Therefore, no attempt was made to "decomposite" residue values to simulate residues that might be present in the single servings contained in the PDP composite sample.

2) Although PDP uses multi-residue methods to simultaneously analyze various pesticides on a crop sample, occasionally, for various reasons, there are no entries for some pesticides on some samples. In such instances, it was assumed that those pesticides with no entries had zero residues.

3) All residue analyses are subject to the limitations of the sensitivity of the analytical methods. Many of the samples analyzed are reported as being below the limit of reliable detection of the analytical method. It is usual practice in Agency assessments to assume that residues in non-detectable samples are present at ½ the limit of detection (LOD) of the analytical method in samples that were potentially harvested from treated fields. Thus, for purposes of estimating residues in samples reported as <LOD, a proportion of the samples equal to the estimated percent crop treated is assigned a residue level of ½ LOD and the remaining samples, which are assumed to come from untreated crops, are assigned a residue value of zero. This procedure becomes problematic for a cumulative assessment. It is not enough to simply estimate the percent crop treated for each of the pesticides in the cumulative assessment; it is also important to consider the potential for co-occurrence of residues of multiple residues on the same crop. A strength of the present example is that it accounts for co-occurrences in single samples if they are detectable. In the case of the OP pesticides we assessed the impact of incorporating ½ the LOD for non-detects in the cumulative assessment. The food portion of the OP assessment was conducted using the two extreme default assumptions: all non-detects = 0, and all non-detects = ½ LOD for the chemical with the greatest number of detectable residue findings. The most prevalent detected chemical was chosen because it is reasonable to assume that chemical would also have the greatest number of residues below the limit of detection. The result of this comparison confirmed that the assumption of zero values for all non-detects did not significantly impact on the results at the higher end of the

cumulative exposure distributions. It is our judgment that similar results would be found in the case of the N-methyl carbamates although we have not tested this at this time.

4) The sample-by-sample method of summing of residues relied on the PDP sampling procedures to adequately capture the temporal and geographic variations in uses of pesticides. This procedure recognizes that the PDP sampling protocols are designed in such a way as to reflect the foods available to the public for consumption in different regions of the country and throughout the year.

5) This assessment uses residue data collected over a ten year period, 1994 through 2003. The primary reason for this is to maximize the number of food commodities in the assessment but this raises issues of lack of co-occurrence. Co-occurrence in the food is important from the standpoint of all the food consumed in the same time period. It is not readily obvious if it is appropriate to model exposure based on bananas grown in 1994 and apples grown in 1998. A related choice in selection of residue data was to include all available data for a given commodity from this time period. This includes data sets that span a time period of at least one year to 4 years data.

6) In chemical specific dietary exposure assessments the Agency routinely translates residue data from one food commodity to related ones if the pesticide use patterns are similar on these commodities (USEPA, 1999b). For example, data on cantaloupes is often used as surrogate data for watermelons and other melons. For a cumulative assessment, in which a grower has a choice of several chemicals from the cumulative assessment group, these translations of data become more difficult to make. In the current case study, translations of the residue data were made using the surrogation scheme in HED SOP 99.3 in order to ensure representation of the maximum number of commodities possible. The cross walk between crops is presented in Table II.C.1-1 in Appendix II.C.1.

5. Food Consumption Data

For this assessment food consumption is being modeled on the USDA Continuing Survey of Food Intakes by Individuals (CSFII) , 1994 to 1998. The consumption survey is included as an integral component of the DEEM-FCID software. The CSFII 1994-1998 contains survey data on 20,607 participants interviewed over two non-sequential days. It contains a supplemental children's survey conducted in 1998 in which an additional 5,459 children, birth through 9 years old, were added to the survey.

DEEM-FCID™ also has integrated new USDA/EPA recipes for conversion of foods reported eaten in the survey to food commodities on which residue data are available. These recipes, which are available to the public, replace proprietary recipes used in previous versions of DEEM.

In this preliminary NMC CRA separate assessments were conducted on the general U.S. population and sub-populations as represented in the CSFII 1994-1998. The current assessment reports on the U.S. General population and the following sub-populations: infants < 1 years, children 1-2 years, children 3-5 years, children 6-12 years, youth 13-19 years, adults 20-49 years, adults 50+ years and females 13-49 years.

6. Estimation of Acute Exposure Using DEEM-FCID™ Software

Residue distribution files, or average residue values for highly blended commodities, were input in the DEEM-FCID™ software for a Monte Carlo analysis.

The Monte Carlo analysis was conducted by an iterative process of multiplication of residue concentrations on foods, expressed in index chemical equivalents, by one-day consumption of these foods, as reported by all individuals in CSFII. This process used all individuals reporting in the consumption survey for both days of the survey and the exposures were calculated as mg/kg body wt/day.

The use of DEEM for dietary exposure analysis has been described in the presentation of our previous dietary assessments of the OP pesticides to the panel. The detailed functioning of the program has also been described in a previous SAP presentation (*Dietary Exposure Evaluation Model (DEEM™) and DEEM™ Decompositing Procedure and Software*) available on the previously referenced FIFRA Scientific Advisory Panel website.

7. Results

Table I.C.3 summarizes the results of a cumulative dietary exposure assessment for N-methyl carbamates on food commodities. Exposures and MOEs (Margins of Exposures) are presented for the U.S. General population and the following sub-populations: infants < 1 years, children 1-2 years, children 3-5

years, children 6-12 years, youth 13-19 years, adults 20-49 years, adults 50+ years and females 13-49 years. The summary results are provided for three points in the distribution of exposures estimated: the 95th percentile, 99th percentile, and 99.9th percentile of exposure. The exposure values and MOEs are expressed in terms of index-chemical equivalents

8. Summary

The cumulative dietary exposure due to the use of N-methyl carbamate chemicals on food crops was assessed using residue monitoring data collected by PDP. Oxamyl was selected as the index chemical and the residue values for the other N-methyl carbamate chemicals were converted to index chemical equivalents by the Relative Potency Factor method. Residue data were collected on approximately 65 food commodities monitored by PDP between the years of 1994 and 2003. Food processing factors were applied to specific chemical/commodity pairs to extend these data for use on more food forms. The PDP residue data were further extended to other commodities identified as reasonable for surrogation of pesticide residue data per HED SOP 99.3

The residue data were compiled as distributions of cumulative residues of index chemical equivalents that were, after adjustment for processing, summed on a sample-by-sample basis. These residue distributions were combined with a distribution of daily food consumption values *via* a probabilistic procedure to produce a distribution of potential exposures for the general U.S. population and sub-populations. The results of this assessment are shown in Table I.C.3. An analysis of the relative exposure contribution from foods for children 1 to 2 years at or above the 99.8 percent exposure level is presented in Table I.C.4.

Table I.C.1. N-methyl Carbamates, Code Letters and RPFs

Code Letter	Chemical	RPF	Parent Chemical
A	Carbaryl 1 Naphthol	0.12	Carbaryl
B	Aldicarb Aldicarb sulfone (Aldoxycarb) Aldicarb sulfoxide	3.32	Aldicarb
C	**Oxamyl (Index Chemical)** Oxamyl oxime	**1**	**Oxamyl (Index Chemical)**
D	Formetanate hydrochloride	1.89	Formetanate hydrochloride
E	Methomyl	0.38	Methomyl
F	Carbofuran 3-Hydroxycarbofuran	1.19	Carbofuran
G	Propoxur	0.09	Propoxur
H	Methiocarb	0.14	Methiocarb
I	Thiodicarb	0.7	Thiodicarb
J	Pirimicarb	0.02	Pirimicarb

Table I.C.2. Permissible Crop Translations for Pesticide Monitoring Data

Commodity Analyzed	Commodity translated to...	Comments
Potato	Subgroup 1-C	
Carrot	Subgroup 1-A or 1-C	
Head Lettuce	Cabbage, Chinese cabbage Napa (tight headed varieties), Brussels sprouts, radicchio	All have a head morphology best represented by lettuce. All are in Subgroup 5-A except radicchio (4-A).
Broccoli	Cauliflower, Chinese broccoli, Chinese cabbage bok choy, Chinese mustard, kohlrabi	Broccoli better represents these heading, thickly stemmed and/or more branching cole crops than spinach does.
Spinach	Subgroup 4-A, Subgroup 5-B and Subgroup 4-B (except celery and fennel unless a strong case can be made)	Celery and fennel typically are excluded since residues may be higher in these crops due to the whorled, overlapping petioles which may retain spray residues.
Green Bean	Subgroups 6-A and 6-B	
Soybean	Subgroup 6-C	
Tomato or bell pepper	Group 8	All are fruiting vegetables[2].
Cucumber	Subgroup 9-B	All are cucurbit vegetables; residues in melon and pumpkin expected to be lower because of removal of rind
Cantaloupe or Winter squash	Subgroup 9-A and pumpkin	
Orange	Group 10	Fruit will be peeled before analysis by PDP.
Apple or Pear	Group 11	All are pome fruits.
Peach	Group 12, except cherries (sweet and tart)	All are stone fruits.
Grape	Kiwifruit	Based on similar cultural practices.
Wheat	Group 15, except corn, rice, or wild rice	All are small grain crops or closely related thereto
Milk	Meat	Metabolism study must indicate that residues in meat, fat, and meat-by-products will likely be equal to or lower than residues in milk. If dermal use is allowed on beef cattle, then it must be permitted and used on dairy cattle as well.

[1] The reviewer should take special note of the requirement that the use scenarios be similar among translatable commodities. The mode of application (e.g., foliar, preplant) should be the same. The label application rates and preharvest intervals should be similar. The percent of crop treated also should be similar (or lower for the crop in the "translated to" column). All residues of concern should be measured or accounted for including conjugates. Tolerances and field trial residues are to be similar, as well. The reviewer should also check with the Biological and Economic Analysis Division (BEAD) to insure that use scenarios are similar, and that agricultural practices do not differ substantially.

[2] The reviewer should be careful in checking for comparable residue levels because of weight differences in tomatoes and peppers.

Table I.C.3. Summary of Probabilistic Analysis of Distribution of the Cumulative Dietary Exposures and Risk from Use of N-methyl carbamate Chemicals on Food Crops

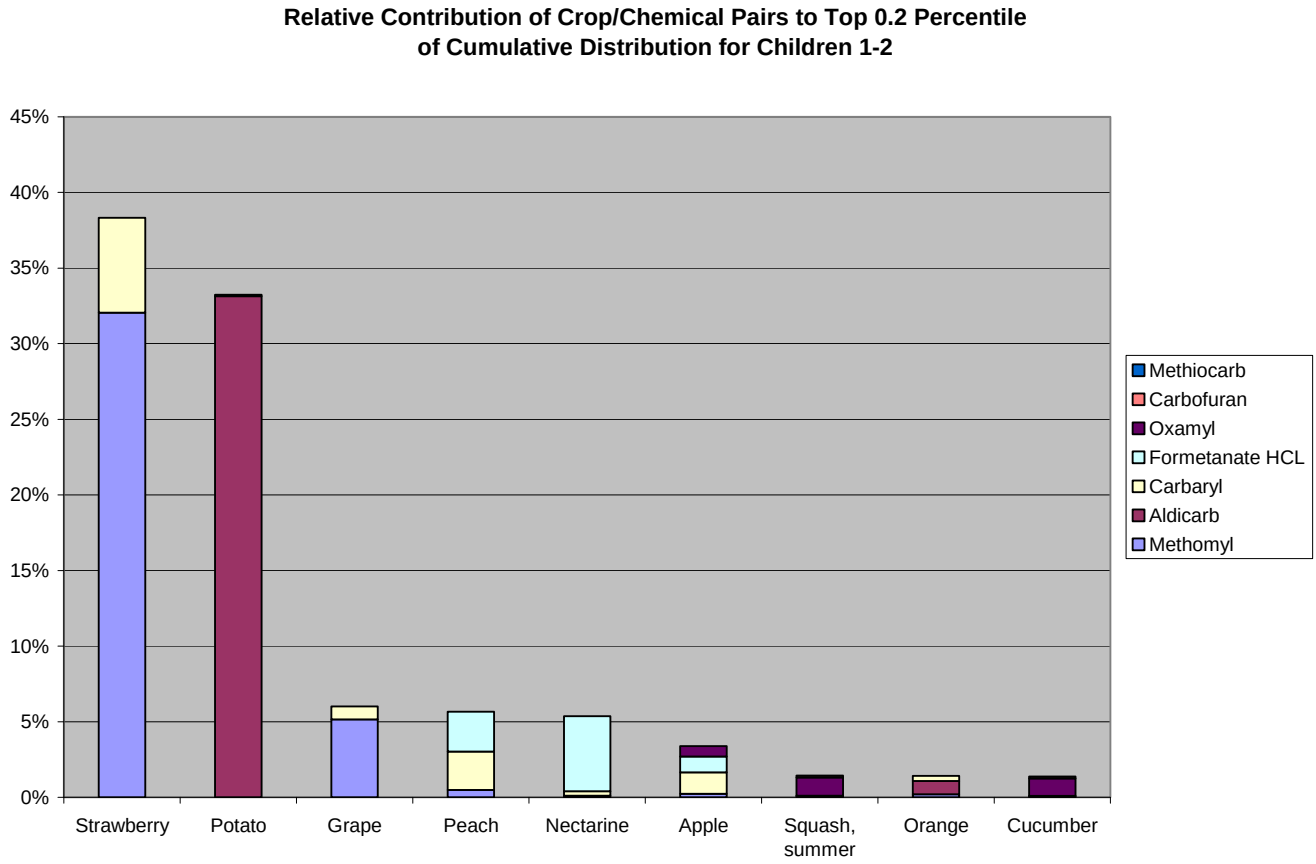
	95th Percentile		99th Percentile		99.9th Percentile	
Population	**Exp**	**MOE**	**Exp**	**MOE**	**Exp**	**MOE**
U.S. Population	0.000047	2979	0.000290	483	0.001619	86
All infants < 1 yrs	0.000041	3415	0.000189	741	0.001288	109
Children 1-2 yrs	0.000143	979	0.000745	188	0.003773	37
Children 3-5 yrs	0.000128	1094	0.000696	201	0.003368	42
Children 6-12 yrs	0.000070	2000	0.000426	329	0.002278	61
Youth 13-19 yrs	0.000032	4375	0.000231	606	0.001428	98
Adults 20-49 yrs	0.000034	4118	0.000221	633	0.001279	109
Adults 50+ yrs	0.000044	3182	0.000254	551	0.001273	110
Females 13-49 yrs	0.000036	3889	0.000235	596	0.001346	104

Exposure is in mg/kg/day of the index chemical

Table I.C.4. Relative Exposure Contribution from Foods for Children 1 To 2 Years Old (At 99.8% Risk Level and Above)

Food	**Percent**
Strawberry	38.3%
Potato	33.2%
Grape	6.0%
Peach	5.7%
Nectarine	5.4%
Apple	3.4%
Squash, summer	1.4%
Orange	1.4%
Cucumber	1.4%
Total	**96.2%**

Figure I.C.1. Relative Contribution of Crop/Chemical Pairs to Top 0.2 Percentile of Cumulative Distribution for Children 1-2



D. Cumulative Risk from Carbamate Pesticides in Drinking Water

The Food Quality Protection Act (FQPA) of 1996 requires the Agency to assess the risks from different pesticides having a common mechanism of action, focusing on the likelihood that a person will be concurrently exposed to multiple pesticides from multiple sources (food, drinking water, and residential uses). Ideally, data to support the drinking water portion of this exposure assessment would consist of information on multiple pesticides, and their transformation products, collected from sufficient drinking water sources throughout the U.S. and at a sufficient frequency to reflect the spatial and temporal patterns of pesticide occurrence in water. The great diversity of geographic-, climatic-, and time-dependent factors that affect the levels of pesticide residues in water creates unique challenges in characterizing drinking water exposure. The Office of Pesticide Programs (OPP) must rely on both available monitoring data and modeling to develop sufficient data for use in the exposure assessment.

Because of similarities in use (both the N-methyl carbamates and organophosphates are insecticides), hazard endpoints (acute or short term), and exposure requirements (estimates of peak concentrations and time-series distributions), the Agency used the same methods for estimating surface water exposure in the N-methyl carbamate (NMC) drinking water assessment as it did for the organophosphate (OP) cumulative risk assessment (CRA). These methods have already been presented to the FIFRA Scientific Advisory Panel (FIFRA SAP, 2002).

Unlike the OP pesticides, the N-methyl carbamates also are likely to reach ground-water sources of drinking water. The Agency presented a conceptual model for ground water exposure and a plan for evaluating the capability of three ground water models to estimate carbamate concentrations to the FIFRA SAP in February, 2005. The ground water exposure estimates for this NMC CRA are based on this plan and on feedback from the SAP (FIFRA SAP, 2005).

For the preliminary NMC CRA, the Agency focused on both surface- and ground-water sources of drinking water that represent the high-end of anticipated cumulative carbamate exposures in sources of drinking water.

1. Problem Formulation

The approach for assessing drinking water exposure accounts for the fact that pesticide concentrations found in drinking water are not random, but are in large part determined by the amount, method, timing and location of pesticide application, the physical characteristics of the watersheds and/or aquifers in which the community water supplies (CWS) or private wells are located, and other environmental factors, such as rainfall, which can cause the pesticide to move from the location where it was applied. The choice of data and tools to estimate the drinking water exposure component of the cumulative exposure depends upon the questions to be answered and the expected exposure in water.

a. Drinking Water Exposure Estimates Required for the Carbamate Cumulative Assessment

For the N-methyl carbamate group, the toxicity endpoint of concern results from short-term exposure (acute effects). To adequately characterize the potential impacts of pesticide residues in drinking water, the estimated residue concentrations need to reflect a sufficient reporting frequency in time to capture peak concentrations. Because pesticide loads in surface water tend to move in relatively quick pulses in flowing water, the frequency sufficient to reliably capture peak concentrations is on the order of daily sampling for surface water sources of drinking water. However, pesticide concentrations in ground water are the result of longer-term processes and less frequent sampling is sufficient to characterize peak ground water concentrations.

The drinking water exposure assessment needs to account for the potential for any or all of the carbamates included in the cumulative assessment group (Table I.D.1) to occur together in drinking water sources. To realistically estimate exposures, the assessment must take into account those factors (crop uses, pest pressures, timing of application, etc.) which determine whether more than one carbamate pesticide can occur together in time and place. Although multiple carbamate pesticides may be registered for use on the same crop, they may not necessarily be used at the same time. While monitoring data could provide real-time estimates of co-occurrence, it needs to be able to account for all of the potential carbamates used in the monitoring area, be of sufficient frequency to capture short-term peaks in pesticide exposure, particularly in surface water, and span sufficient years to capture the impact of variability in use and weather patterns on pesticide transport.

Table I.D.1. N-methyl carbamate use patterns and availability of national monitoring data

Pesticide	Use pattern likely to result in water exposure?	Availability of national water monitoring data?
Aldicarb (including sulfoxide, sulfone degradates)	Yes (agricultural uses)	Yes: NAWQA, Reservoir monitoring; state monitoring
Carbaryl	Yes (agricultural and residential uses)	Yes: NAWQA, Reservoir monitoring
Carbofuran	Yes (agricultural uses)	Yes: NAWQA, Reservoir monitoring; state monitoring
Formetanate	Yes (agricultural uses)	No
Methiocarb	Limited impact from limited use	Some limited NAWQA monitoring
Methomyl	Yes (agricultural uses)	Yes: NAWQA, Reservoir monitoring
Oxamyl	Yes (agricultural uses)	Yes: NAWQA, Reservoir monitoring
Pirimicarb	Limited impact from indoor uses, limited outdoor use	No
Propoxur	No (indoor uses)	Some limited NAWQA monitoring
Thiodicarb (including methomyl degradate)	Yes (agricultural uses)	No

While several of the NMC pesticides have major environmental degradates, only the sulfoxide and sulfone degradates of aldicarb have a common mechanism with the CAG and are included in the NMC CRA. Thiodicarb breaks down rapidly into methomyl.

b. Nature of Carbamate Exposure in Drinking Water Sources

This section briefly summarizes the nature of expected carbamate exposure in drinking water sources based on individual chemical assessments (aggregate exposure), available water monitoring data, and published literature on the potential impact of conventional drinking water treatment processes on carbamates in water.

Re-registration eligibility documents (REDs), Interim REDs (IREDs), or draft ecological risk assessments are available for all of the NMC pesticides in Table I.D.1 except for pirimicarb (available on the USEPA OPP web site at:

http://cfpub.epa.gov/oppref/rereg/status.cfm?show=rereg)

These individual assessments indicate that seven of the carbamates – aldicarb, carbaryl, carbofuran, formetanate, methomyl, oxamyl, and thiodicarb – have the potential to reach drinking water sources based on use and chemical fate and transport properties. Propoxur has been detected in a few, predominantly non-agricultural monitoring sites in the USGS NAWQA monitoring program, presumably from outdoor crack-and-crevice uses. However, current use is of such limited extent that propoxur is not expected to contribute to the carbamate cumulative load in drinking water sources. Similarly, when the Agency gathered usage information on the NMC pesticides for the regional cumulative drinking water exposures, usage of methiocarb and pirimicarb were of such a limited extent that they did not factor into the NMC cumulative exposure for drinking water.

Seven NMC pesticides (aldicarb and its degradates, carbaryl, carbofuran, formetanate, methomyl, oxamyl, and thiodicarb) are likely to reach surface water sources of drinking water via runoff or sediment transport, and have been detected in monitoring studies. Two carbamates – aldicarb and carbofuran – are likely to reach and persist in ground water sources of drinking water, especially in shallow aquifers. Three other carbamates – carbaryl, methomyl, and oxamyl – may also reach ground water, but are not likely to persist.

The most extensive source of national water monitoring data for pesticides is the US Geological Survey (USGS) National Water Quality Assessment (NAWQA) program, which includes seven of the carbamates in its list of pesticides (Table II.D.2). The NAWQA program focuses on ambient water rather than drinking water sources, is not specifically targeted to pesticide use areas, and its sampling frequency (generally

weekly or bi-weekly during the use season) isn't sufficient to provide reliable estimates of peak pesticide concentrations in surface water. However, the program does provide a good understanding on a national level of the expected occurrence of pesticides in flowing water bodies that may be representative of drinking water sources. The monitoring data are better indicators of the nature of occurrence of pesticides with widespread use rather than pesticides that are limited to a few crops or pests. A detailed description of the pesticide monitoring component of the NAWQA program is available on the NAWQA Pesticide National Synthesis Project (PNSP) web site (http://ca.water.usgs.gov/pnsp/).

A summary of the first cycle of NAWQA monitoring from 1991 to 2001 indicates that the seven carbamate pesticides included in the monitoring study were not frequently detected in the NAWQA study units (Table I.D.2). Carbaryl and carbofuran were the most frequently detected carbamate pesticides in streams and ground water, reflecting the broader use patterns of these particular insecticides. In most instances, maximum reported detections of the carbamates were in the single parts per billion or sub-parts per billion range.

As expected, co-occurrence of carbamates in the monitored water samples reflects use patterns. Carbaryl and carbofuran are the most common carbamates occurring together in the NAWQA sampling; up to three different carbamates have been detected in the same surface water samples in the NAWQA study units. Although less commonly observed, more than one carbamate were also detected in a small number of ground water samples. More detailed summaries of the USGS NAWQA monitoring data can be found in Appendix II.D.1.

Table I.D.2. Summary of carbamate detections in the USGS NAWQA study, 1991-2001 (provisional data published by USGS in 2003).

Pesticide	Agricultural Land Use			Mixed Land Use			Urban Land Use		
	% detect	Max ug/L	95th %ile	% detect	Max ug/L	95th %ile	% detect	Max ug/L	95th %ile
Surface Water Monitoring 1									
Aldicarb	0.2%	0.5	nd	0%	Nd	nd	0%	nd	nd
Carbaryl	9.2%	5.2	nd	15.4%	0.5	nd	43.8%	5.2	0.3
Carbofuran	9.6%	7.0	0.04	3.3%	0.7	nd	2.1%	0.1	nd
Methiocarb	0.1%	0.1	nd	0%	Nd	nd	0%	nd	nd
Methomyl	1.6%	0.7	nd	0.3%	0.3	nd	0%	nd	nd
Oxamyl	0.8%	0.2	nd	0%	Nd	nd	0%	nd	nd
Propoxur	0.2%	0.1	nd	0.2%	0.2	nd	0.2%	0.3	nd
Ground Water Monitoring 2									
Aldicarb (incl. degradates)	0.3%	1.8	nd	0.1%	0.1	nd	0%	nd	nd
Carbaryl	0.4%	0.02	nd	0.8%	0.5	nd	1.6%	0.03	nd
Carbofuran	1.6%	1.3	nd	0.4%	0.2	nd	0.7%	0.09	nd
Methiocarb	0%	nd	nd	0.1%	0.03	nd	0%	nd	nd
Methomyl	0.1%	0.04	nd	0.1%	0.1	nd	0.2%	0.4	nd
Oxamyl	0.8%	2.1	nd	0.1%	0.03	nd	0.2%	0.3	nd
Propoxur	0.1%	0.06	nd	0.1%	0.06	nd	0.2%	0.3	nd

1 Martin et al, 2003; http://ca.water.usgs.gov/pnsp/pestsw/Pest-SW_2001_Text.html
2 Koplin & Martin, 2003; http://ca.water.usgs.gov/pnsp/pestgw/Pest-GW_2001_Text.html

NAWQA and other surface-water monitoring programs show that pesticide concentrations in surface water are highly variable in location and in time. This is particularly true for insecticides, such as the carbamates, where usage is often in response to specific pest pressures, which are likely to be concentrated in some areas but not in others and in some years but not necessarily every year. In addition to variable use patterns, carbamate concentrations in surface water are influenced by local soil, hydrology, and weather patterns and by the timing of rainfall events in relation to pesticide use.

While aldicarb has not been detected frequently or in high concentrations in ground water in the NAWQA program, extensive monitoring by others (registrant, state and local governments, universities) shows that, under certain conditions, aldicarb residues (parent and degradates) can occur in ground water and private wells at concentrations as high as several tens to several hundred parts per billion (Table I.D.3).

Label changes for aldicarb now restrict use from certain areas (such as the northeastern states and Wisconsin) and add well-setbacks in Florida. While the extent of aldicarb contamination in ground water is less today than it was in previous decades, it is also less well characterized in most areas. In addition, total aldicarb residues (primarily the sulfoxide and sulfone transformation products) can persist in ground water for years or decades after its use. Twenty years after aldicarb use on Long Island, NY, was halted, aldicarb residues are still the most frequently detected pesticide compounds in ground water (Suffolk County Dept. of Health

Services, 2000). A summary of state monitoring data for the N-methyl carbamates can be found in Appendix II.D.2.

Table I.D.3. Summary of aldicarb detections in ground water monitoring data collected from available ground water monitoring data.

Region (State w/ Highest Recent Detection)	Monitoring data since 1990			Monitoring data representing Drinking Water		
	max conc (ug/L)	95th %ile (ug/L)	70th %ile (ug/L)	Conc (ug/L)	Location	Date of DW value
Northwest	2.1	0.8	0.6	2.1	ID	Max conc since 1990
Southwest	7.2	7.1	6.7	6.4	CA	Max conc since 1997
Northern Great Plains	65	53	9.5	9.7	WY	Max conc since 1992
Lower Midwest	N/A	N/A	N/A	N/A	N/A	No reported detections
North-central	83	24	6.8	23	WI	Max conc since 1992
Northeast	187	24	8.0	24	RI	Max conc since 1994
Southeast and Mid-south	21	20	3.6	20	AL	Max conc since 1990
Florida	55	26	8.5	44	FL	Max conc since 1993

A similarly extensive body of ground water monitoring data exists for carbofuran. Like aldicarb, the extent of monitoring for carbofuran in ground water has decreased in recent years, so current impacts are not as well documented. However, several inferences can be drawn from the body of studies. Targeted ground water monitoring studies show a clear pattern of carbofuran movement into ground water, with maximum detections in the same range as that reported for aldicarb. Because transport to ground water typically takes longer than transport to surface water, measured concentrations of carbofuran in ground water may represent usage that occurred years before the samples were collected. As with aldicarb, carbofuran will also persist in ground water for long periods of time after use has been discontinued. This is particularly true for slightly acidic to acidic ground water because carbofuran is stable to hydrolysis (the major route of degradation in ground water) at pH values of 6.0 or less. The parent aldicarb is less susceptible to alkaline hydrolysis (10% loss after 30 days); however, both the sulfone and sulfoxide degradates hydrolyze rapidly at alkaline pH's (1 to 3 days at pH 9).

EPA' s review of available laboratory and field monitoring data (Appendix II.D.3) indicates that conventional water treatment processes such as coagulation, sedimentation, and conventional filtration will not reliably remove or transform the N-methyl carbamates in drinking water sources. Lime softening and activated carbon filtration can be effective in removing the NMC pesticides. With the exception of parent aldicarb, lime softening processes will break down N-methyl carbamates through

alkaline-catalyzed hydrolysis. Sorption on activated carbon using granular activated carbon (GAC) or powdered activated carbon (PAC) appears to be at least partially effective in removing N-methyl carbamates from drinking water (percent removal ranges from 20 to 38% for aldicarb and oxamyl to 60 to 80% for carbofuran, carbaryl, and methiocarb). Other treatment methods, such as chlorination, chloramination, chlorine dioxide, and potassium permanganate, are only effective in oxidizing N-methyl carbamate compounds containing a methylthio group (CH3-S-), e.g., methiocarb and aldicarb. These compounds are expected to oxidize to sulfoxide and sulfone carbamates that hydrolyze rapidly at alkaline pH values. The Agency estimates that lime softening is used on 7% or less of community ground water systems serving populations of 10,000 or less and less than a third of systems serving more than 10,000 people (USEPA, 2001b). Carbon filtration is used on less than half of the large community water systems, with decreasing percentages of smaller systems using GAC or PAC (USEPA, 2001b). For the NMC CRA, the Agency will qualitatively consider the impacts of conventional drinking water treatment on specific carbamate pesticides in CWS water supplies (both surface- and ground-water). However, the Agency must also consider untreated water concentrations for private ground water wells since these private wells generally do not include any form of treatment.

c. Summary

The goal of the drinking water exposure assessment is to provide estimates of distributions of carbamate residues (concentrations in drinking water) that account for:

- ❑ daily and seasonal variations in residues over time associated with time of application(s) and runoff/leaching events (surface water concentrations are expected to be more variable in time than ground water concentrations)
- ❑ year-to-year variations related to weather patterns, pest pressures, and use
- ❑ variability in residues from place to place, resulting from the source and nature of drinking water and from the regional / local factors (soil, geology, hydrology, climate, crops, pest pressures, usage) that affect the vulnerability of those sources
- ❑ the potential for co-occurrence of more than one carbamate in location and time only when this is likely to happen

2. Conceptual Model

Risk is a function of both hazard and exposure, and estimation of the exposure portion for drinking water requires data on concentrations of the pesticides in the drinking water and consumption of drinking water for different demographic populations on a daily basis. Drinking water is locally derived and concentrations of pesticides in source water fluctuate over time and location for a variety of reasons. Pesticide residues in water fluctuate daily, seasonally, and yearly as a result of the timing of the pesticide application, the vulnerability of the water supply to pesticide loading through runoff, spray drift and/or leaching, and changes in the weather. Concentrations are also affected by the method of application, the location and characteristics of the sites where a pesticide is used, the climate, and the type and degree of pest pressure.

While monitoring data provide a picture of the occurrence of carbamate pesticides in drinking water resulting from variable use in selected locations, the data alone are not sufficient for use in the cumulative drinking water exposure assessment. This section describes the planned approach to estimate cumulative carbamate residues in drinking water using models and evaluating the estimates against available monitoring data.

Based on the needs of the probabilistic cumulative exposure assessment and the information from monitoring data, OPP designed a drinking water assessment that provides multiple years of daily residue concentrations from drinking water sources in regions where high carbamate use coincide with vulnerable drinking water sources. This approach will use a conceptual model similar to that used for the organophosphate (OP) CRA, expanding it to include vulnerable ground water sources.

a. Regional Screening Approach for Vulnerable Sources of Drinking Water

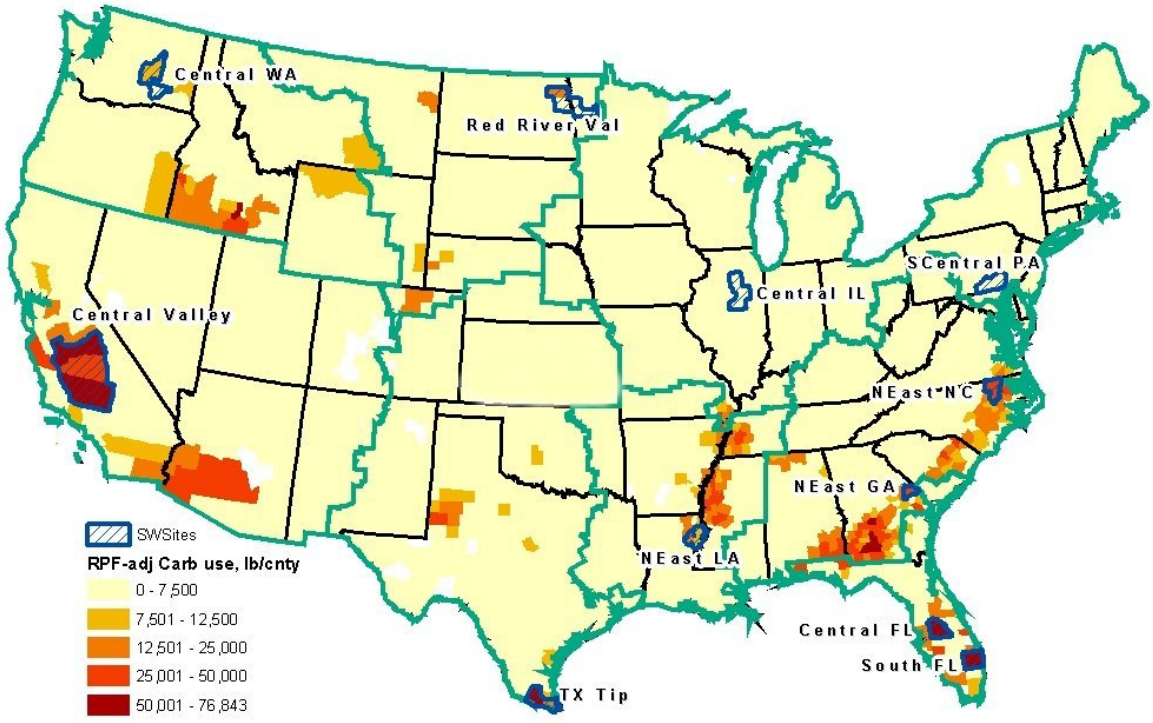
Drinking water exposure will vary locally as a result of to pesticide use, agricultural practices, nature and vulnerability of drinking water sources, and weather patterns. Thus, in the preliminary NMC CRA, the water exposure assessment focused on specific geographic areas of relatively high carbamate use in a manner that would be realistically protective of all carbamate use areas. To facilitate the regional screening approach, the Agency adapted a modification of the USDA Farm Resource Region map (Heimlich, 2000) as a framework for focusing the cumulative assessment (Figure I.D.1). By providing general groupings according to similarities in key environmental factors affecting runoff and leaching, such as precipitation, irrigation practices, and soil types, these farm resource regions provided a framework for identifying one or more locations which represent an area of the greatest concern for drinking water exposure in each region. In this way, the Agency chose a set of locations to represent vulnerable drinking water sources throughout the US.

OPP selected locations where carbamates in drinking water sources are likely to be of greatest concern based on total carbamate use and vulnerability of the drinking water sources. For each region, the Agency used the estimated carbamate cumulative distribution from the vulnerable water source to represent the drinking water portion of the dietary exposure estimate for the entire population in that region. In other words, the Agency initially assumed that everyone in the region is drinking from the same vulnerable water source. If carbamate levels in water from these vulnerable sites are not major contributors to the total regional cumulative exposure, then the Agency can reasonably conclude that drinking water exposures will not be a concern in other less vulnerable areas. If drinking water exposure from one or more of these vulnerable sites is a significant contributor to the total cumulative exposure, then additional refinements may be necessary to characterize the extent of the potential exposure.

For the cumulative assessment, the Agency considered exposure from both surface- and ground-water sources of drinking water. In both cases, the Agency is simulating potential exposure to sensitive populations in a geographic sense. Surface-water sources of water consisted of source water from small reservoirs in predominantly agricultural watersheds with relatively high carbamate use. Ground-water sources of water were shallow private wells located in highly permeable soils in high carbamate use areas. The conceptual models for these sources are described in the following sections.

Although carbaryl has outdoor residential uses that could contribute to the cumulative drinking water source load, the Agency focused on the agricultural contributions because the relative potency factor for that compound (0.12) is much lower than that of aldicarb (3.32), which turns out to be the major driver in the regional water exposure estimates because of its relative potency.

Figure I.D.1. Carbamate cumulative risk assessment regions for drinking water exposure assessment showing high carbamate use areas and regional surface water exposure sites.



b. Conceptual Model for Surface Water Sources of Drinking Water

The Agency bases its drinking water exposure assessment for surface-water sources on a small reservoir in an agricultural watershed. An analysis of available monitoring data indicate that such reservoirs are likely to be among the most vulnerable surface drinking water sources (FIFRA SAP, 1998; USEPA, 1999c, 2000b/Part A). The NMC CRA focuses on watershed-scale impacts from multiple carbamate uses occurring in multiple fields in a watershed. This is the same approach the Agency used for the OP CRA (see Figure I.D.2).

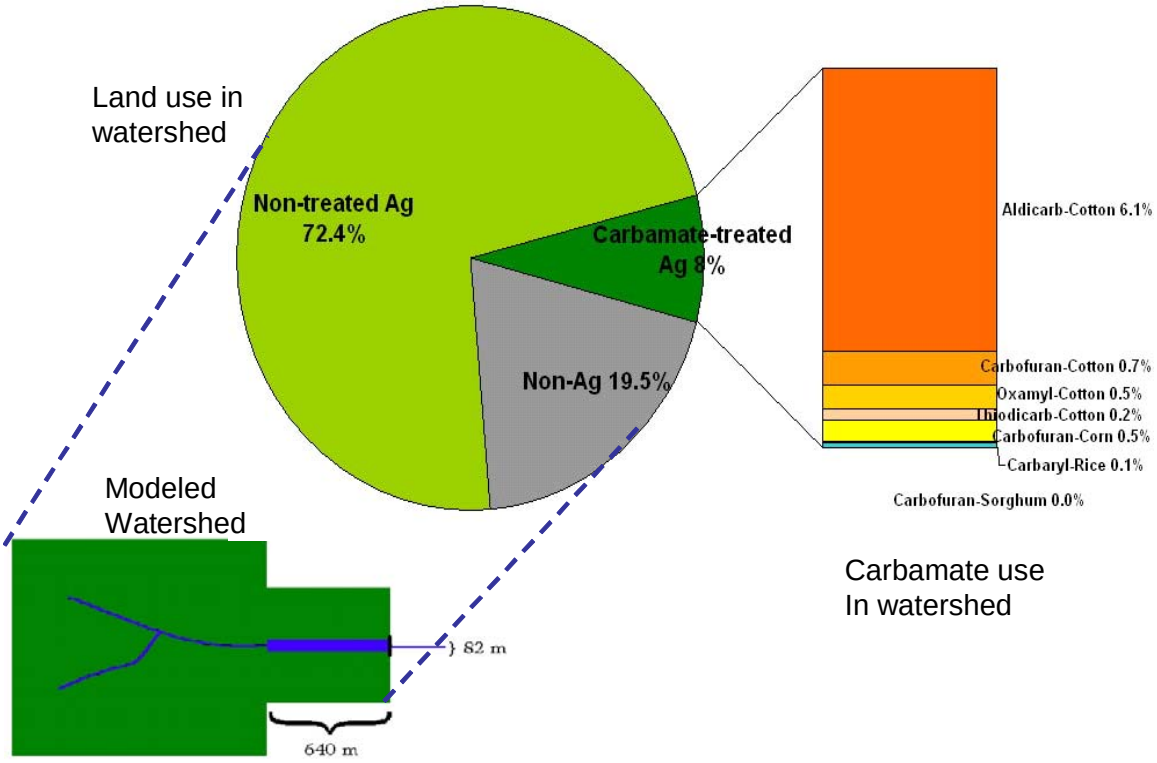
The conceptual model the Agency uses for determining co-occurrence of N-methyl carbamate pesticides in surface water sources of drinking water is based on the amount and timing of pesticide use in the watershed that contributes to the surface water source. County- or multi-county level pesticide use information, based on agricultural chemical use surveys, serves as a surrogate for identifying the potential for co-occurring carbamate uses in the same location. Timing of the applications, along with pesticide persistence and transport characteristics, reflect the relative potential of multiple carbamates to occur together in time. The relative proportions of each carbamate used in the watershed area are based on the amount applied in a given year (a function of the rate and frequency of

application, combined with the crop area treated at that scale), pesticide fate and transport properties that affect the amount of pesticide available at the surface for runoff, the runoff susceptibility of the soil, and the timing, amount, and frequency of rainfall.

For the regional assessments, the Agency identified one or more high-use areas within each region that coincided with potentially vulnerable surface water sources (described in the analysis plan). The Agency determined the potential for co-occurrence in surface water sources by determining carbamate use in the high-use counties as reported in the USDA National Agricultural Statistics Service (USDA NASS) and the Doane's databases (described in the analysis plan and in Appendix II.D.4).

For the watershed approach, OPP estimated pesticide concentrations over time (30-year simulation) for each crop-carbamate combination. The temporal distributions allowed the Agency to determine the likelihood of co-occurrence of the N-methyl carbamates in water over time. The Agency used regional crop areas (based on USDA Ag Census data, as described in USEPA, 2000b/Part B) and acre treatments to adjust the estimated daily concentrations for each of the carbamates for the portion of the watershed that is treated by a particular carbamate. These crop-adjusted concentrations are converted to a concentration equivalent for the index chemical (in this case, oxamyl) and combined into a single set of daily cumulative concentrations (spanning multiple years) for each region.

Figure I.D.2. Conceptual model for surface water sources of drinking water illustrating how multiple carbamate uses are proportioned in the watershed.



For exposure from surface water sources of drinking water, the Agency used estimated concentrations derived for the source water from the reservoir, assuming no treatment effects. The Agency has no reason to expect that the standard drinking water treatment process will result in more toxic transformation products, so the assumption of no treatment effects for the NMC pesticides provides an upper bound on the estimated exposures at the tap water.

c. Conceptual Model for Vulnerable Ground Water Sources of Drinking Water

The potential for pesticide movement to ground water sources of drinking water depends on a variety of factors, including hydrologic properties of the overlying soil and vadose zone that affect downward movement of water and chemicals, travel time through the unsaturated zone to ground water, aquifer properties (conductivity, porosity, depth, type, location of recharge area), the leaching potential of the pesticide (persistence and mobility), and the type of well drawing water for drinking purposes (Focazzio et al, 2002). While these factors may vary geographically and cause certain wells in one region to be more vulnerable than those in another region, EPA is basing its ground water exposure assessment on private rural wells which draw water from a shallow, unconfined aquifer. In general, such drinking water sources tend

to be more vulnerable and provide estimates of drinking water exposure that are realistic for a population that lives in agricultural areas and relies on such wells for drinking water.

Figures I.D.3 and I.D.4 illustrate the conceptual model the Agency used to estimate pesticide transport to private wells. The pesticide is applied to the soil surface or plant canopy and precipitation or irrigation may move the pesticide through the soil profile and into a saturated zone. These transport processes are simulated with each of the three models—PRZM, RZWQM, and LEACHP— though each model performs the simulation calculations differently (FIFRA SAP, 2005).

All models simulate a shallow surficial aquifer with a water table at 3.5 m below the surface. Well-screen length is assumed to be 1 meter and starts at the water table, extending from 3.5 to 4.5 meters. The concentration in the well is the average saturated pore water concentration across the one-meter length of the screen (Figure I.D.3).

Degradation occurs at different rates through the soil profile. Generally, faster degradation from microbial processes occurs in the top of the profile and decreases with depth. In the conceptual model, the Agency assumed that aerobic metabolism occurs in the top 25 cm, with rated declining linearly from 20 cm to 1 meter. Below a meter, only abiotic processes (in this case, hydrolysis) are considered to be in effect. Pesticides may degrade in the upper reaches of the soil profile by both abiotic and biotic processes and in the lower vadose zone and aquifer by abiotic processes (Figure I.D.4). This is consistent with the default arrangement in the RZWQM model; for PRZM and LEACHP, input files were set up to reflect this effect.

For some pesticides, well setbacks (Figure I.D.3) are specified by state or federal regulations. For such cases, the additional travel time for a pesticide to reach a drinking water well and the degradation that occurs during that time is taken into consideration by a plug flow model.

Figure I.D.3. Depiction of general ground water scenario concept used for estimating pesticide concentrations in drinking water

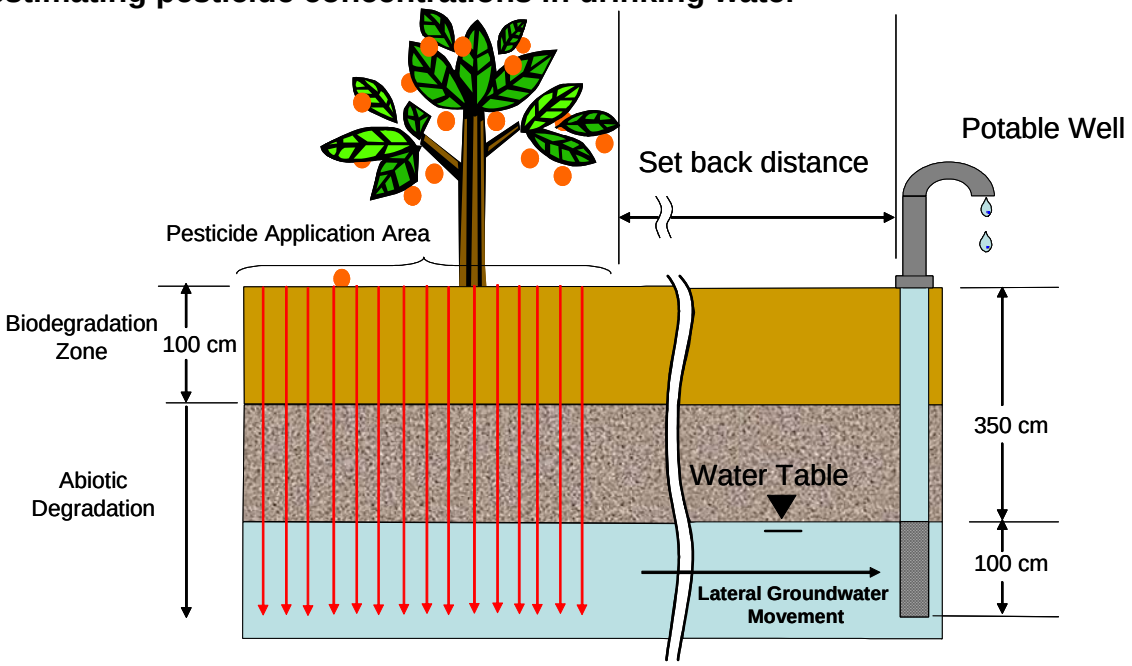
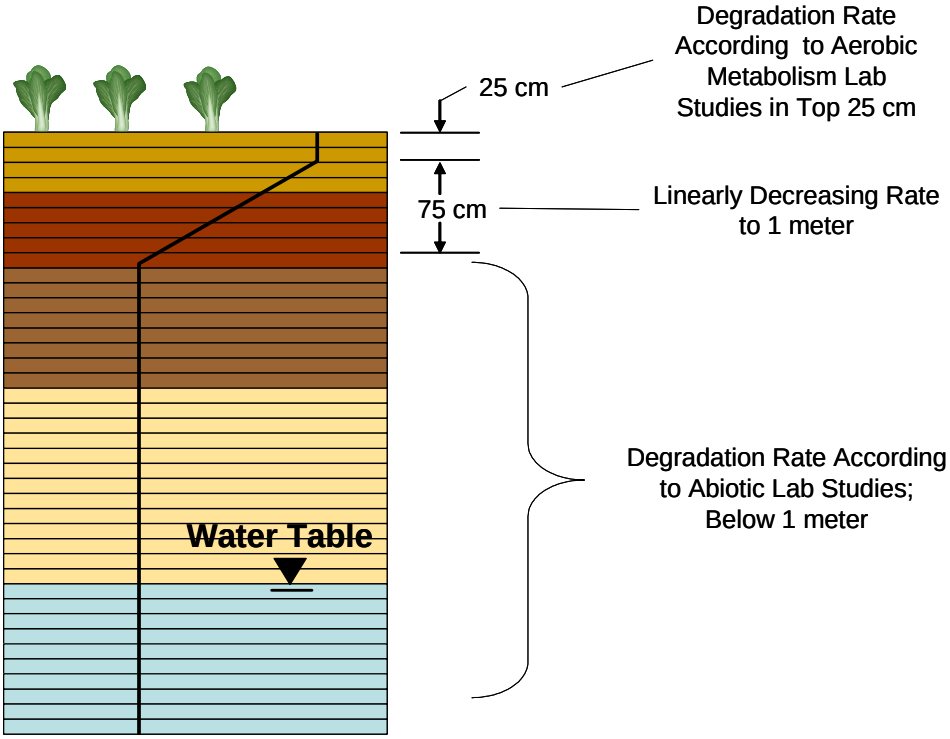


Figure I.D.4. Conceptual model for handling pesticide degradation though the soil and vadose zone



While N-methyl carbamate concentrations in ground water are affected by pesticide use, rainfall, and soil conditions, the response time between an application or leaching event and detection in ground water is not as rapid as it is for surface water. Carbamate concentrations in ground water are less likely to reflect same-season or same-year events. Pesticide fate properties and available monitoring data indicate that several of the N-methyl carbamates in the cumulative group are likely to persist in acidic ground waters. In addition, cumulative exposure in ground water is likely to reflect past as well as current uses.

Available monitoring data, primarily from the USGS NAWQA program, confirm that more than one carbamate in the cumulative action group may occur together in ground water (see the drinking water exposure section of the case study). The Agency believes that co-occurrence in ground water will result when more than one carbamate are used at different times on the same crop, on different crops in rotation on the same fields, or on different crops grown on adjacent fields. Because of lags in travel time and in reported persistence of some carbamate residues in ground water, EPA will consider historical usage in addition to current use on the surface above the aquifer recharge area.

3. Analysis Plan

This section provides a brief description of the methods of analysis the Agency used in generating the cumulative N-methyl carbamate concentrations in drinking water sources for use in the cumulative dietary exposure assessment.

a. N-methyl Carbamate Properties

The predicted persistence and movement of each of the carbamate pesticides in the environment are based on environmental fate and transport studies submitted by the pesticide registrants as a requirement of registration and/or re-registration. Inputs for the water models are based on the individual chemical assessments. Table I.D.4 summarizes the dominant persistence and mobility characteristics of each of the N-methyl carbamates included in the drinking water exposure assessment. Appendix II.D.5 provides the specific chemical inputs used in the water exposure models. The NMC common assessment group includes the sulfoxide and sulfone degradates of aldicarb. No other degradates for the other NMC pesticides had the same common mechanism, except for thiodicarb, which transforms into methomyl. For aldicarb, the Agency used half-life values for the combined aldicarb residues (parent plus degradates) and the sorption value for the most mobile of the degradates.

Table I.D.4. Summary of N-methyl carbamate fate and transport properties.

Pesticide	Persistence / Degradation Pathway	Mobility / Sorption
Aldicarb (including sulfoxide and sulfone degradates)	**Field**: Aerobic soil metabolism (55 d half-life); pH-dependent hydrolysis for degradates **Water**: Aerobic aquatic metabolism (12 d half-life)	Kd = 0.12 mL/g (Koc = 10 mL/g)
Carbaryl	**Field**: Aerobic soil metabolism (12 d half-life); hydrolysis (12 d @ pH7, 0.1 d @ pH9) **Water**: Aerobic aquatic metabolism (30 d half-life); pH-dependent hydrolysis	Koc = 196 mL/g
Carbofuran	**Field**: Hydrolysis (28 d @ pH7); aerobic soil metabolism (321 d half-life) **Water**: Hydrolysis	Koc = 36 mL/g
Formetanate HCl	**Field**: Aerobic soil metabolism (6 d half-life); hydrolysis (24 d @ pH7,9) **Water**: Aerobic aquatic metabolism (13 d half-life); hydrolysis	Koc = 340 mL/g
Methomyl	**Field**: Aerobic soil metabolism (79 d half-life); alkaline hydrolysis (30 d @ pH9) **Water**: Aerobic aquatic metabolism (7 d half-life); hydrolysis	Koc = 24 mL/g
Oxamyl	**Field**: Hydrolysis (8 d @ pH7, 0.1 d @ pH9); aerobic soil metabolism (20 d half-life) **Water**: Hydrolysis; aerobic aquatic metabolism (40 d); anaerobic aquatic metabolism (7 d)	Koc = 6 mL/g
Thiodicarb (degrades to methomyl)	**Field**: Aerobic soil metabolism (2 d half-life); hydrolysis (32 d @ pH7, 0.5 d @ pH9) **Water**: Aerobic aquatic metabolism (3 d half-life); anaerobic aquatic metabolism (<1 d); pH-dependent hydrolysis	Koc = 485 mL/g

b. Identifying Regional Exposure Scenarios

The selection of specific locations for regional drinking water assessments involves several steps. First, the Agency identified the high carbamate usage areas within each region. To account for the differences in toxicities among the carbamates, OPP adjusted the county-level estimates of pounds of each carbamate by their respective relative potency factors before summing the total pounds of carbamate use. Thus, the adjusted usage map (Figure I.D.1) reflects the areas of greatest use of the most potent of the carbamates.

Next, OPP identified the types of drinking water sources in each high usage area. The Agency used a spatial dataset that describes water use for all the counties in the continental US (USGS, 1998) to determine the dominant source of drinking water – (1) public supply served by surface water, (2) public supply served by ground water, or (3) domestic self-supplied drinking water (primarily private wells). The Agency overlaid the public surface water supply data with the adjusted carbamate use map to identify counties in which high carbamate use coincided with surface water sources of drinking water. The county also looked at locations of drinking water intakes (based on SDWIS data) for vulnerable surface water sources. For private wells, the Agency overlaid the domestic

drinking water supply data with carbamate use to identify those counties where high carbamate use coincided with populations drinking from private wells.

The final step in choosing regional locations for modeling is to assess the vulnerability of drinking water sources within the high usage area within the region. For surface water sources of drinking water, OPP compared relative vulnerabilities of the areas based on average annual runoff, average 2-month runoff (beginning of the growing season), and average soil loss, as developed by the USDA Natural Resources Conservation Service (Kellogg et al, 1997). The regional surface water scenario sites are shown in Figure I.D.1 and summarized in Table I.D.5.

Table I.D.5. Regional drinking water exposure sites and dominant carbamate uses.

Region	Exposure scenario sites (1)	Dominant use crops	Carbamates used
Southeast	Northeast NC (SW, GW), eastern GA (SW), southwestern GA (GW)	Cotton, peanuts, tobacco, pecans	Aldicarb, carbaryl, carbofuran, methomyl, oxamyl
Florida	South FL (SW), central FL (GW, SW)	Citrus, sweet corn, sugarcane, cucumber, pepper	Aldicarb, carbaryl, carbofuran, methomyl, oxamyl, thiodicarb
Mid-south	Northeast LA (SW)	Cotton, corn, sorghum	Aldicarb, carbofuran, oxamyl, thiodicarb
North / north central	South central PA (SW), central IL (SW)	Apples, corn, peaches, sweet corn, alfalfa, pumpkin, potato, beans	Carbaryl, carbofuran, formetanate HCl, methomyl, oxamyl, thiodicarb
Lower Midwest	Southern tip of TX (SW)	Grapefruit, cotton, vegetables	Aldicarb, carbofuran, formetanate HCl, methomyl, oxamyl
Northern Great Plains	Red River Valley (SW)	Potatoes, sugar beets, wheat	Aldicarb, carbaryl, carbofuran, oxamyl
Northwest	Central WA (SW, GW)	Potatoes, apples, cherries, beans, carrots, onions	Aldicarb, carbaryl, carbofuran, formetanate HCL, methomyl, oxamyl
Southwest	CA Central Valley (SW)	Citrus, stone fruit trees, cotton, melons, grapes, tomatoes, various cole, root, tuber vegetables	Aldicarb, carbaryl, carbofuran, formetanate HCl, methomyl, oxamyl

(1) SW = surface water scenario site; GW = ground water scenario site

For ground water sources of drinking water, OPP compared relative ground water vulnerabilities of the high carbamate use areas based on a variety of sources, including Nolan et al (2002), USGS NAWQA reports, USGS Ground Water Atlases, USDA/NRCS county soil datasets (SSURGO), and other state/local information. Where available, the Agency used monitoring data to help identify specific site, soil, and hydrologic properties that might serve as indicators of vulnerable ground water conditions. For the preliminary NMC CRA, the Agency identified vulnerable ground water (private well) scenarios in central FL along the

central ridge, the coastal plain of eastern North Carolina and southwestern Georgia, representing highly vulnerable aquifers with high carbamate use. The Agency also developed a ground water exposure scenario for central Washington, reflective of high carbamate use in the north and west.

c. Regional Usage

The regional exposure areas of interest consist of multi-county areas that encompass the vulnerable drinking water source in high carbamate use areas. OPP collected information on the target crops, estimated carbamate usage, and timing of application for these multi-county areas.

The drinking water exposure assessments require information on crop use, pounds applied, application rate, number of applications, percent of crop treated, and application timing. Much of this information is not easily available or does not exist at the geographic scale needed for the exposure assessment. As a result, OPP used the best available information to provide the best regional estimates for the carbamate pesticide-crop combinations that actually occur in scenario areas. Because county-level pesticide usage data is based on surveys and is uneven in quality, OPP created county clusters that surrounded the initial scenario areas shown in Figure I.D.3. The Agency also used multiple data sources and multiple years of data to improve the robustness of the use data.

For each regional scenario site, OPP used USDA National Agricultural Statistics Service (USDA NASS) and Doane's databases to estimate usage (acres planted, total pounds used, percent of crop treated, application rate, and number of applications) for each carbamate and crop reported in the use cluster. Usage was averaged for the years 1998 through 2002. The Agency identified those carbamate-crop uses that accounted for at least 95% of the total carbamate usage in the scenario area.

Once the crop / chemical combinations were identified in a given area, OPP used USDA crop profiles and typical planting/harvesting dates and various other sources to identify most likely windows of application for each carbamate use. Typically, all the carbamates discussed here target multiple pests or ones that can occur multiple times during a given crop's growing season, so applications often occur over a broad time period. For the case study, OPP systematically selected the beginning of the most active window for the initial application date of each carbamate. Where multiple applications were identified, the Agency spread those evenly over the most active window. Details of the methods and resulting regional usage information can be found in Appendix D.II.4.

d. Surface Water Exposure Assessment

The Agency estimated the daily drinking water exposure from surface water sources using the simulation models PRZM (Pesticide Root Zone Model) and EXAMS (EXposure Analysis Modeling System). With PRZM/EXAMS modeling for a drinking water reservoir, the Agency can:

- ❑ Account for potential co-occurrence of carbamates by modeling all uses in a region/area, as described in the conceptual model
- ❑ Combine daily time series over multiple years (using 30 years of recorded weather data) to account for year-to-year variations in weather and to separate peak concentrations that are not likely to occur together in time
- ❑ Estimate peak concentrations (on a daily time step); adjustments to pesticide use inputs ("typical" rates, frequencies) can reflect estimated concentrations in a "typical" year
- ❑ Model vulnerable surface water sources in regions to reflect spatial variations in crops, use, weather, soil, hydrology
- ❑ Adjust for crop area, acres treated

A detailed description of the models is available from the OPP Water Models web site:

(http://www.epa.gov/oppefed1/models/water/index.htm)

The model estimates daily pesticide concentrations in surface water sources of drinking water (a reservoir) using local soil, site, hydrology, and weather characteristics along with pesticide application and agricultural management practices, and pesticide environmental fate and transport properties. The input parameters are specific for each carbamate-crop scenario in each region. For instance, in the eastern North Carolina exposure site representing the Southeast region of the US, the cotton, peanut, and tobacco scenarios consist of properties for soils on which the crops are grown in the coastal plain of North Carolina. The weather data used in the simulations come from 30 years of weather collected at a NOAA weather station in Raleigh/Durham, just west of the scenario area. Appendix II.D.6 provides details on the models and site-specific inputs for the surface water exposure.

The cumulative assessment focuses on the probability or likelihood of concurrent exposure to multiple pesticides from food, water, and residential use. It is unlikely that the exposure to the highest (peak) concentrations for multiple carbamates in a use area will occur at the same time. Thus, the cumulative assessment uses average application

rates, average numbers of applications, and estimates of acres treated to adjust concentrations. The implications of these assumptions are discussed in the risk characterization section.

PRZM is a field-scale model, while the cumulative water assessment focuses on watershed-scale impacts (i.e., the contributions of multiple carbamate uses on multiple crops occurring in multiple fields in a watershed). The Agency used PRZM to model multiple fields in a watershed. While this approach provides a more realistic depiction of multiple chemical usage in a watershed, it provides no spatial context for those fields. It also assumes that the runoff from each of those fields goes into the reservoir.

To adapt PRZM for this watershed approach, OPP adjusted the estimated pesticide concentrations generated for each crop-carbamate combination to account for the portion of the watershed that is treated by a particular carbamate. This was accomplished a cumulative adjustment factor (CAF):

- The carbamate-crop combination was modeled with PRZM/EXAMS, using the region-specific usage, application timing, soil, site, and weather data. The result is a time-series of daily pesticide concentrations in a reservoir spanning a 30-year period.

- Each daily concentration is adjusted by the fraction of the watershed that is in the crop being modeled. The fraction is calculated by dividing the acres of crop grown in the multi-county region by the total acres in that region (percent crop area).

- The daily concentrations are then adjusted by the fraction of acres of the crop treated by the particular carbamate. The fraction is calculated by dividing the acres of crop treated by the total crop acres in the multi-county region (percent crop treated).

The resulting CAF-adjusted concentrations for each crop-carbamate combination must be converted to a concentration equivalent for an index chemical. The RPF-adjusted concentrations were combined into a single set of daily cumulative concentrations (spanning multiple years) for each region. The concentrations were normalized to an index equivalent by multiplying each of the daily concentrations by the relative potency factor (RPF) for the respective carbamate pesticide. This normalized output for each crop-carbamate combination was summed day-by-day to give a single time series of potential combined water residues for the region. The resulting carbamate cumulative drinking water exposure was provided as a cumulative daily time series over 30 years.

In summary, within each region, a residue file was generated by PRZM-EXAMS for each crop-carbamate combination which was reported

in the county or counties selected for the assessment. This day-by-day residue file was modified by the CAF specific to that crop-carbamate combination and the relative potency factor for that pesticide. Then, the modified residue files for all crop-carbamate combinations for that location were summed across days to give a distribution of combined daily residues in drinking water.

e. Ground Water Exposure Assessment

EPA used three models to estimate carbamate concentrations in ground water sources of drinking water: Pesticide Root Zone Model (PRZM), Root Zone Water Quality Model (RZWQM), and Leaching Model for Pesticides (LEACHP). These models were selected based on their availability and capability for addressing the needs of the cumulative exposure assessment. The background materials for the February 2005 FIFRA SAP provide more information on the models. These materials are available from the SAP web site listed in the references. Specifically, the ground water exposure assessment must account for:

- **Variations in Residues Over Time**: Pesticide residues in ground water are likely to fluctuate less drastically than residues in surface water; however, the model estimates need to provide a concentration time series.

- **Variations in Residues Over Location**: As with the surface water assessment, EPA will focus on regional ground water sources of drinking water that are expected to be among the most vulnerable to carbamate contamination based on soil, geology, hydrology, climate, crops, pest pressures, and usage.

- **Co-occurrence**: USGS monitoring shows that co-occurrence of carbamates, though infrequent, does occur in ground water. Therefore, EPA estimated ground water concentrations for multiple carbamate pesticides in ground water, based on regional usage data.

Based on feedback and recommendations from the February 2005 FIFRA SAP (FIFRA SAP, 2005), the Agency used these models to estimate pesticide concentrations in the upper 1 meter of a fixed saturated zone (water table) located 3.5 meters below the surface. Neither PRZM nor RZWQM were developed to simulate saturated conditions. A saturated zone can be created in PRZM by setting the field capacity input parameter equal to the porosity. Output concentrations are the average from the top of the saturated zone to a depth 1 meter below the water table. RZWQM scenarios were set up with tile drains and head gates to mimic a near-constant water table depth. Concentrations out of the drain are calculated in RZWQM by taking the average concentration of the overlying saturated zone from tile drain to top of water table.

Appendix II.D.7 provides details on how the models were designed up to simulate water tables and generate estimated concentrations. It also provides site-specific inputs for the ground water model scenarios.

As with surface water, the resulting cumulative distributions from ground water were converted to an index chemical based on the relative potency (RPF) and, then summed for a cumulative ground water distribution. The resulting ground water estimates for the preliminary NMC CRA are based on RZWQM. Appendix II.D.7 includes model comparisons and discussions of differences. The Agency will be consulting with the FIFRA SAP on these comparisons in the August 2005 SAP.

4. Analysis: Carbamate Cumulative Surface Water Exposure

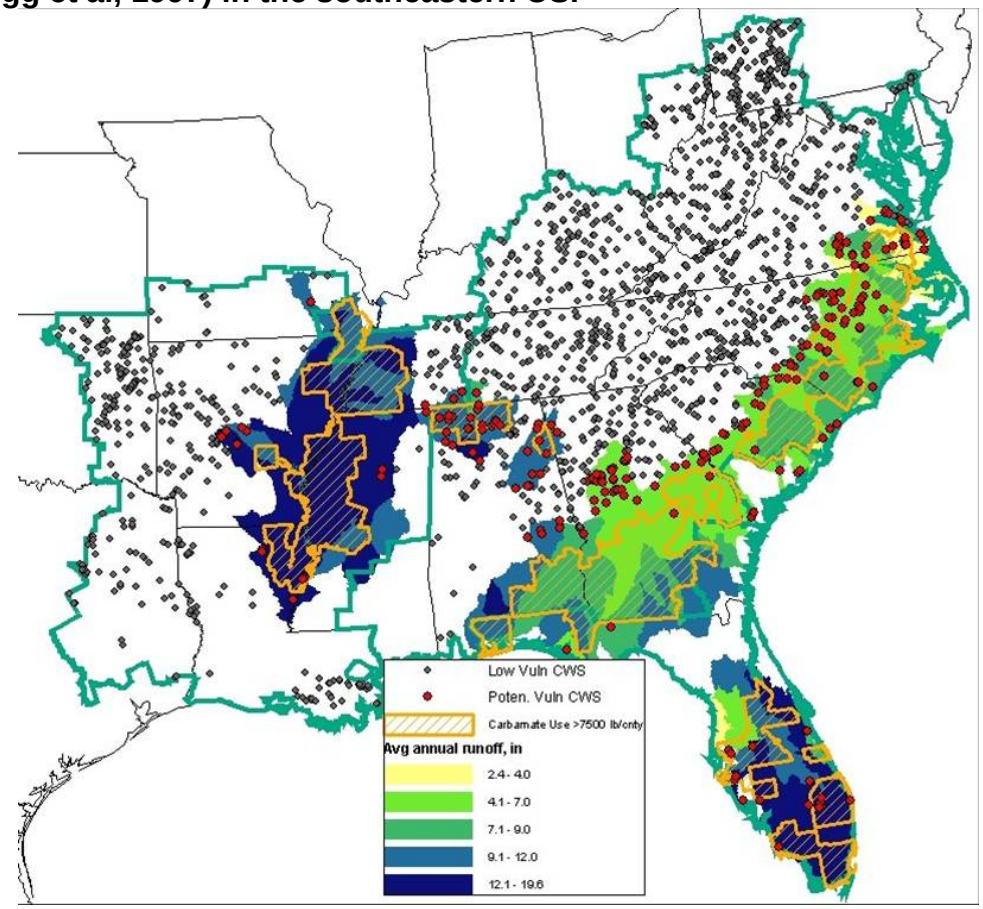
The Agency estimated drinking water concentrations for individual carbamate pesticides and for the cumulative carbamate load for each of the regional surface water scenario sites listed in Table I.D.5. Details and results of these exposure estimates can be found in Appendix II.D.6. The greatest estimated cumulative carbamate concentrations in surface water sources of drinking water occurred in the southeastern part of the United States (Southeast, Florida, and Mid-south regions), with the highest estimated peak concentrations and frequencies of peaks predicted for the northeastern NC site (Table I.D.6). The estimated peak concentrations for the surface water sources are at least one to two orders of magnitude lower than the estimated peaks for the Florida ground water exposure sites.

Table I.D.6. Percentile concentrations for estimated N-methyl carbamate cumulative distributions in the surface water scenario sites (30-year period).

Region/Site	Percentile concentration in ug/L (oxamyl equivalents)						Major contributor
	Max	99th	95th	90th	75th	50th	
Southeast / NC	4.2	0.92	0.20	0.079	0.0047	<0.0001	Aldicarb
Southeast / GA	1.2	0.30	0.072	0.019	0.001	<0.0001	Aldicarb
Florida / Central	1.5	0.24	0.040	0.014	0.0021	0.0004	Aldicarb
Florida / South	1.0	0.23	0.11	0.061	0.021	0.0067	Carbofuran, methomyl, oxamyl
Midsouth / LA	2.3	0.46	0.10	0.041	0.0093	0.0009	Aldicarb
Lower Midwest / TX	0.72	0.27	0.11	0.068	0.028	0.0087	Carbofuran, aldicarb, oxamyl
Southwest / CA	0.30	0.11	0.045	0.026	0.011	0.0053	Aldicarb, methomyl
Northwest / WA	0.18	0.056	0.014	0.0086	0.0048	0.0011	Aldicarb, carbofuran, methomyl, oxamyl
North/ N central / IL	0.13	0.046	0.017	0.0095	0.0026	0.0004	Carbofuran
North/ N central / PA	0.10	0.032	0.012	0.0066	0.0021	0.0006	Carbofuran
Northern Great Plains/ MN-ND	0.017	0.0079	0.0032	0.002	0.0006	0.0001	Aldicarb, carbofuran, carbaryl

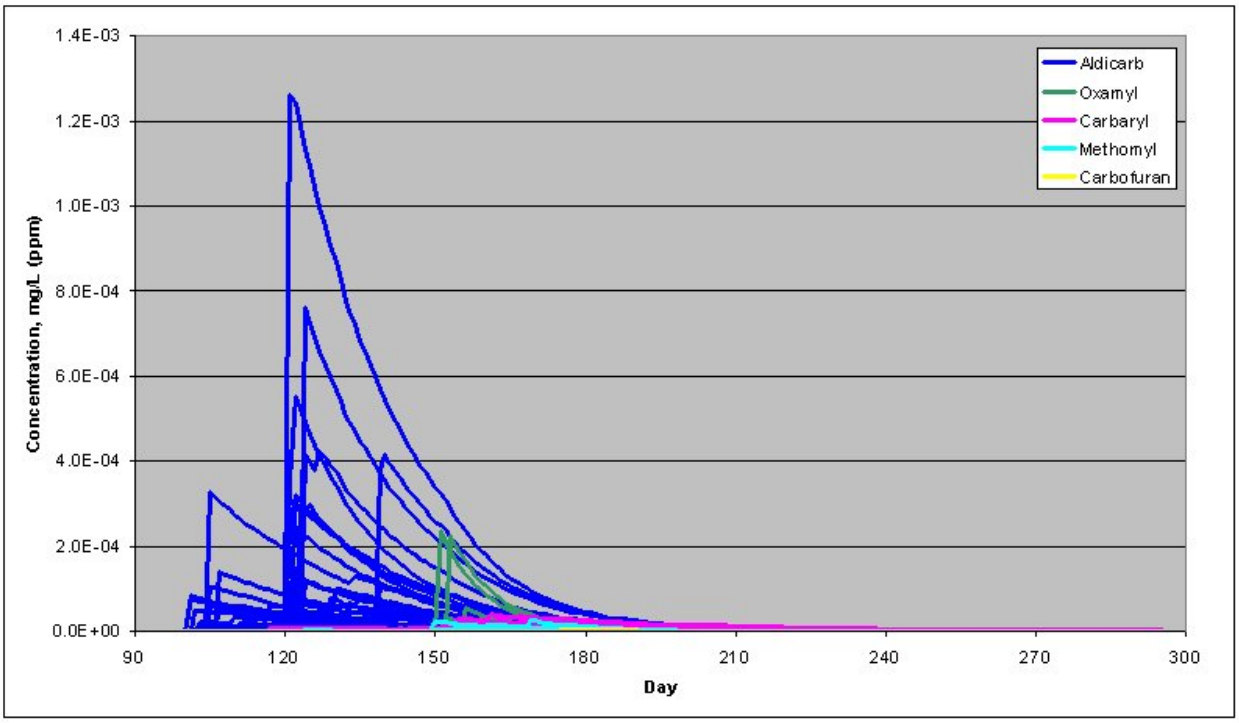
The North Carolina surface water site represents high carbamate use areas along the coastal plain from southeastern Virginia to southeastern Alabama. The dominant carbamate uses in the region are on cotton, peanuts, and tobacco. Many surface water sources of drinking water in the southeastern regions occur where total carbamate use is low (Figure I.D.6). Surface water intakes within the high carbamate use areas of the Southeast region are largely confined to the western side of the coastal plain, with more intakes to the north, in Virginia, North Carolina and South Carolina. The watersheds that are most vulnerable to runoff in the high carbamate use area tend to occur in areas where ground water is the dominant source of drinking water.

Figure I.D.5. Location of surface water intakes (red dots) in relation to carbamate usage (high use areas outlined in orange) and runoff vulnerability (based on Kellogg et al, 1997) in the southeastern US.



Estimated peak concentrations of the individual carbamate pesticides in each of the regional surface water scenario sites were in the sub-parts per billion range, except for aldicarb, which had estimated peaks as high as a single part per billion in the northeast NC site (Figure I.D.7; Appendix II.D.6). The aggregated cumulative exposure to humans will reflect this seasonal pattern seen in Figure I.D.7, with the greatest exposures from drinking water occurring in late spring and summer (May-July), dropping to negligible levels during the rest of the year. In contrast, the cumulative ground water exposures showed a less pronounced seasonal trend, with estimated exposures remaining at elevated concentrations for prolonged periods.

Figure I.D.6. Variability in peak N-methyl carbamate concentrations in surface water from 30 years of time series in North Carolina.



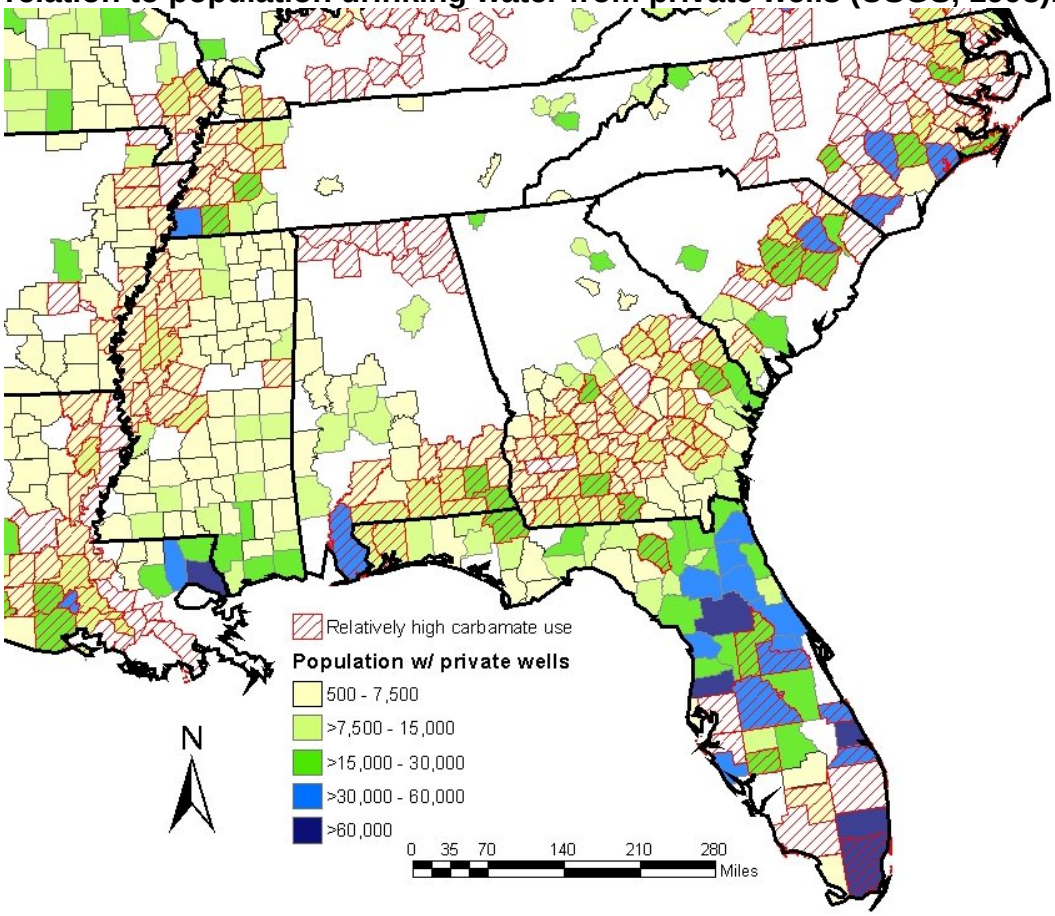
5. Analysis: Ground Water Exposure

Preliminary risk assessments and monitoring data indicate that aldicarb (primarily its sulfoxide and sulfone degradates, which are part of the cumulative assessment group) and carbofuran are the two N-methyl carbamates most likely to reach and persist in ground water sources of drinking water, especially in shallow aquifers. Three other carbamates – carbaryl, methomyl, and oxamyl – may also reach ground water, but are not as likely to persist. Detections of these chemicals in ground water are infrequent. The carbamates are more likely to reach ground water sources of drinking water where ground water is shallow, the soils and overlying vadose zone are highly permeable and/or fractured, and the soils/vadose zone/ ground water system tend to be more acidic. These served as the preliminary criteria for identifying vulnerable ground water sources.

Although monitoring for the carbamates, particularly aldicarb and carbofuran, was more extensive in the late 1980's and early 1990's, before some label and use changes occurred, the body of monitoring data for these chemicals helps identify potentially vulnerable ground water supplies. The highest reported detections of aldicarb residues (parent plus sulfoxide and sulfone degradates) have been in Long Island (NY), the northeastern states, and Wisconsin, where aldicarb is no longer used. Both aldicarb and carbofuran uses in these areas were voluntarily restricted (either uses were cancelled or soil restrictions put in place) in large part because of ground water contamination. Within the current aldicarb use area, the highest reported detections are in Florida and in the southeastern region.

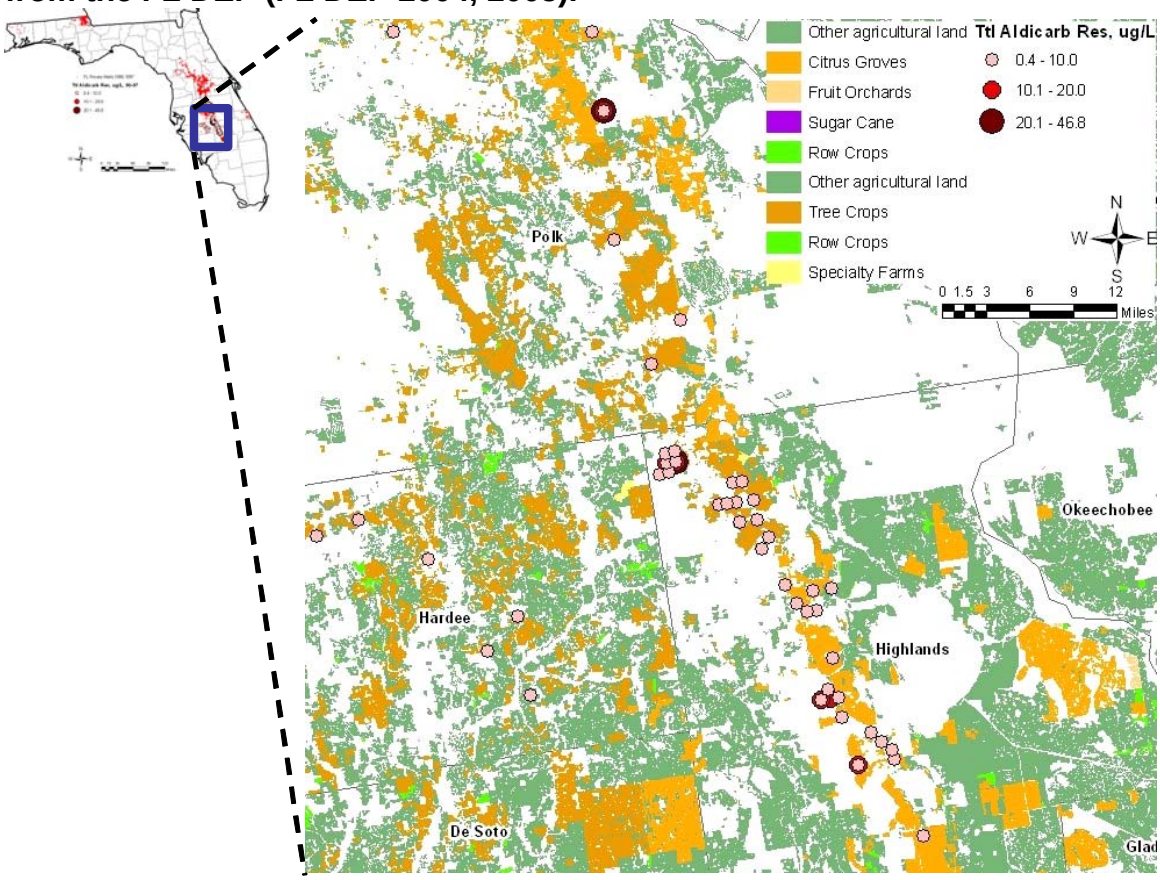
High carbamate use areas occurred in counties where substantial portions of the population obtained their drinking water from private wells along the southeastern Coastal Plain and in Florida (Figure 1.D.8). For the preliminary NMC CRA, the Agency focused on vulnerable ground water supplies in Florida. Based on the conceptual model, the Agency focused on private wells drawing from the surficial aquifer. Additional ground water exposure estimates for the southeast coastal plain and for the northwestern US can be found in Appendix II.D.7.

Figure I.D.7. Location of high carbamate use areas (Thelin & Gianessi, 2000) in relation to population drinking water from private wells (USGS, 1998).



The Florida Department of Environmental Protection (FL DEP, 2005) has been monitoring for aldicarb, aldicarb degradates, carbaryl, carbofuran, carbofuran degradates, methomyl, and oxamyl in private wells across FL for a number of years. Of the NMC pesticides, only aldicarb residues exceed detection limits (see Appendix II.D.2 for discussion). While the frequency of aldicarb detections in the wells is low (1.3% detections), wells with detections follow a distinct spatial pattern, with total aldicarb residues as high as 47 ug/L. The detections are concentrated along the central ridge of Florida in citrus use areas (Figure 1.D.9). Citrus (oranges and grapefruit) is the dominant aldicarb use in this part of Florida (Appendix II.D.4).

Figure I.D.8. Aldicarb detections in private wells related to citrus land use (orange color on map) in central FL. Land use coverage and monitoring data are from the FL DEP (FL DEP 2004, 2005).

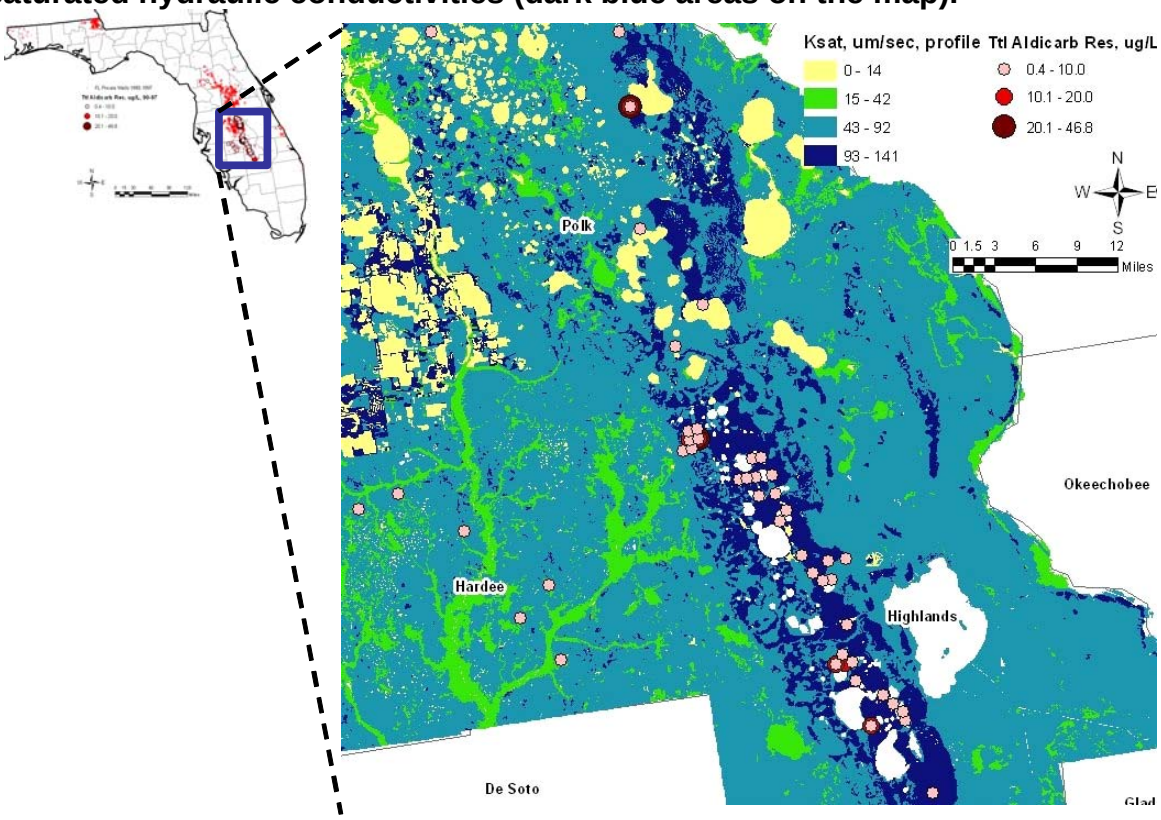


Most of the aldicarb detections in the FL DEP study occurred before 1997, when label changes added well setback requirements for aldicarb use in Florida. Aldicarb cannot be applied within 300 feet of any drinking water well for all soils and uses in FL. For citrus, the setback increases to 1000 feet for highly permeable well-drained soils, unless the well is properly cased. However, an evaluation of available land use coverage and photos indicates that a number of wells with reported detections already had setbacks of at least 300 feet from existing citrus groves. Additionally, FL DEP confirmed that carbon filters have been placed on wells with aldicarb detects (FL DEP, communication, 2005). Therefore, it is difficult to determine the degree to which reductions in aldicarb detections resulted from changes in the label setbacks or from the addition of carbon filters for those wells with previous detections.

While aldicarb detections are associated with citrus land use, not all of the wells in the citrus use area have detections. Wells with detections are predominantly located along the central ridge, which follows a north-northwest to south-southeast pattern through Polk and Highlands counties (Figure I.D.9). An evaluation of county-scale soil data (USDA NRCS, 2005) for Polk, Highlands, and Hardee counties shows that aldicarb detections are associated primarily with

those soils that have high to very high saturated hydraulic conductivities throughout the soil profile (Figure I.D.10). These soils are also identified as excessively or somewhat excessively drained (USDA SSDS, 1993).

Figure I.D.9, Relationship of aldicarb detections in private wells with soils with high saturated hydraulic conductivities (dark blue areas on the map).



While this analysis has not taken into account depth to ground water, characteristics of the vadose zone beneath the soil thickness characterized in the soil survey, or regional variations in precipitation, land use and soil properties related to leaching/downward water movement do provide good indicators of potentially vulnerable shallow ground water sources of drinking water.

The Agency developed ground water scenarios for central Florida citrus using the characteristics of the vulnerable soils identified above. Similar ground water scenarios were developed in the North Carolina Coastal Plain, southwestern Georgia, and central Washington (see Appendix II.D.7 for scenario details). Using typical application rates for the carbamates (Appendix II.D.4), and well setbacks (1000 feet for aldicarb on citrus), the Agency estimated cumulative carbamate concentrations representing vulnerable private wells in Florida, the southeast, and the west. Table I.D.7 summarizes the regional cumulative exposures in ground water used for the preliminary NMC CRA.

Table I.D.7. Characterization of estimated regional N-methyl carbamate cumulative concentrations in ground water/ private wells.

Region	NMC ground water exposure	Major contributors
Florida	Peak concentrations ranged from 40 to 120 ug/L oxamyl equivalents for the FL central ridge	Aldicarb
Southeast	Peak concentrations ranged from 25 to 30 ug/L oxamyl equivalents for highly permeable vadose zone in the southeastern coastal plain (NC, GA)	Aldicarb
West (Northwest, Southwest)	Peak concentrations low to negligible for central Washington	None
North / north-central	No modeled estimates. Anticipated exposure is expected to be lower than surface water estimates because of low carbamate use.	None
Mid-south	No modeled estimates. Predominantly public ground water supply from deep, protected aquifers. Carbamate contamination not expected.	None
Great Plains, Lower Midwest	No modeled estimates. Anticipated exposure is expected to be lower than surface water estimates because of low rainfall, deeper aquifers than in the southeast and Florida	None

The three models the Agency used to estimate NMC residues in ground water – RZWQM, PRZM, and LEACHP – varied in relative ranking of estimated concentrations from region to region (Table I.D.8; more detail in Appendix II.D.7). For the FL central ridge scenario, all three models provided peak estimates of total NMC-cumulative concentrations in ground water that were within a factor of 2 of each other. While RZWQM typically estimated higher peaks in the FL central ridge than the other two models, it also showed more of a seasonal/yearly pattern in concentrations (Figure I.D.10). Yearly patterns were least evident with LEACHP. This may reflect the rapid hydraulic conductivity of the soils on the central ridge or it may be an artifact of modeling parameters. Differences between the three models were greater In the North Carolina scenario, with RZWQM estimates of peak NMC-cumulative concentrations 4 to 7 times greater than PRZM estimates and 8 to 20 times greater than LEACHP estimates. In the Georgia scenario, PRZM estimates were roughly 2 times greater than those of RZWQM. In Central Washington, PRZM estimates were orders of magnitude greater than those of RZQWM. One immediate explanation for the discrepancies is that RZWQM uses a different weather file than does PRZM and LEACHP. Other differences may result from the way each model simulates leaching. The

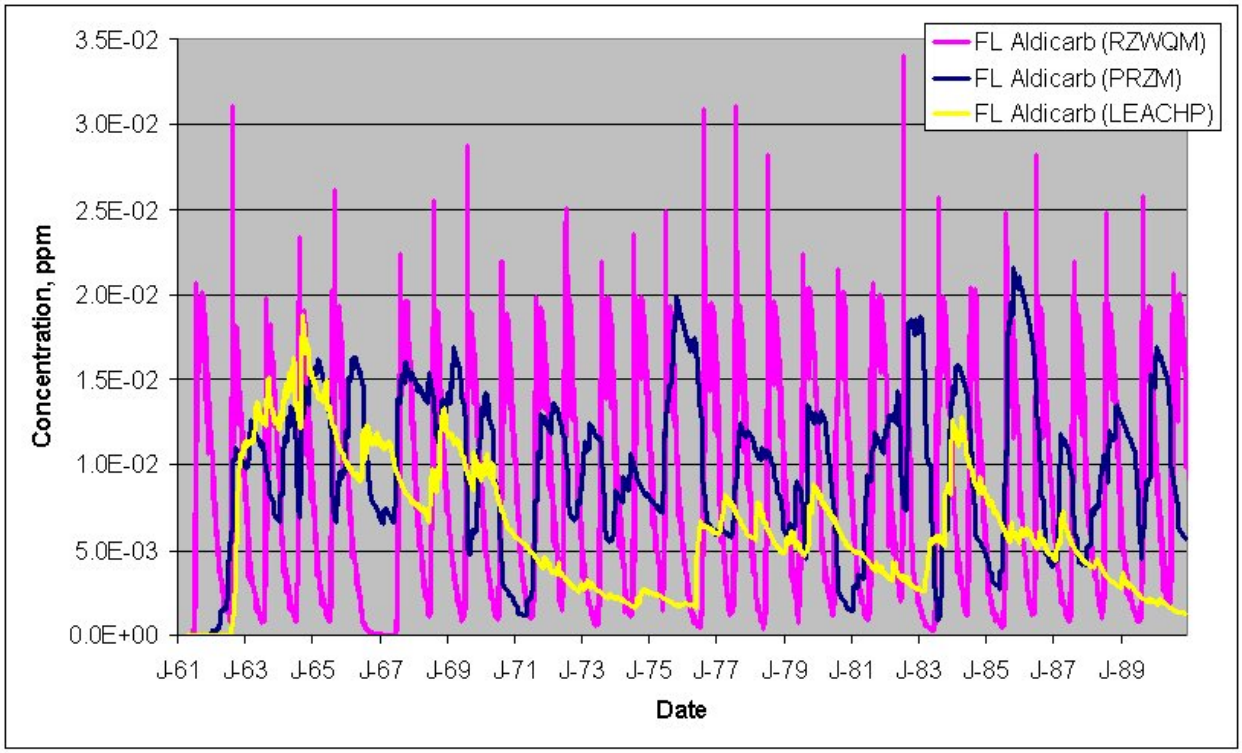
Agency is evaluating the models to determine potential explanations and will be bringing these issues to the August 2005 FIFRA SAP.

Table I.D.8. Comparisons of modeled estimates of regional N-methyl carbamate cumulative distributions in ground water (30-year period)

Model	Percentile concentration in ug/L (oxamyl equivalents)						
	Max	99th	95th	90th	85th	75th	50th
FL Central Ridge							
PRZM	73.0	68.7	59.8	53.3	50.5	44.8	34.2
RZWQM	119.4	70.7	67.1	63.3	60.1	52.6	26.0
LEACHP	66.5	53.5	45.6	41.3	38.0	32.1	20.6
NC Coastal Plain							
PRZM	6.7	6.4	5.5	4.9	4.1	3.4	2.9
RZWQM	29.4	26.8	24.4	23.6	23.4	22.1	19.7
LEACHP	3.6	2.9	2.3	2.0	1.8	1.4	0.9
GA Coastal Plain							
PRZM	5.6	5.3	4.6	4.3	3.9	3.4	2.6
RZWQM	3.0	2.8	2.5	2.2	2.0	1.7	1.0
Central WA							
PRZM	0.006	0.004	0.0007	0.0002	<0.0001	<0.0001	<0.0001
RZWQM	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

The Agency also compared model estimates against monitoring data. Appendix II.D.7 discusses model calibration and comparison with prospective ground water (PGW) monitoring studies. Because of the available monitoring data, the Agency compared estimated peak concentrations of total aldicarb residues with detections found in the FL DEP monitoring data. Estimated peak concentrations of total aldicarb residues ranged between 20 and 35 ug/L using RZWQM, 10 to 22 ug/L using PRZM, and 5 to 19 ug/L using LEACHP (Figure I.D.10). These estimates are comparable to detections reported in the FL DEP monitoring data, where detections of total aldicarb residues ranged from 1 to 47 ug/L. Comparisons with other ground water monitoring studies (Jones et al, 1987; Hornsby et al, 1990) indicate that the models provided estimated concentrations in the same magnitude as those detected in the field (Appendix II.D.7). In the North Carolina cotton/peanuts scenario,

Figure I.D.10. Estimated concentrations of total aldicarb residues in ground water over 30 years from citrus use in Central FL using three models.



The estimated exposures for private wells in FL represents what the Agency believes is the most vulnerable drinking water sources for the N-methyl carbamates based on available monitoring, current use patterns, and known soil and hydrologic conditions. While the concentrations are on the order of several tens of parts per billion, they are on the same order of reported detections in private wells monitored by the state of FL. The estimates represent a small area defined by citrus land use coinciding with highly permeable soils (Figures I.D.8 and 9). Figure I.D.11 shows the resulting distribution of NMC residues for the FL central ridge scenario. Figure I.D.12 compares the estimated NMC cumulative distributions for ground water in the Florida central ridge and the NC and GA coastal plain scenarios with the highest estimated surface water concentrations. The spread in the data represent 30 to 40 years of simulations.

Figure I.D.11. Distribution of estimated oxamyl (blue), aldicarb (pink), and cumulative (dark red) concentrations in a shallow private well in the citrus area of central FL. Cumulative concentration is in oxamyl equivalents.

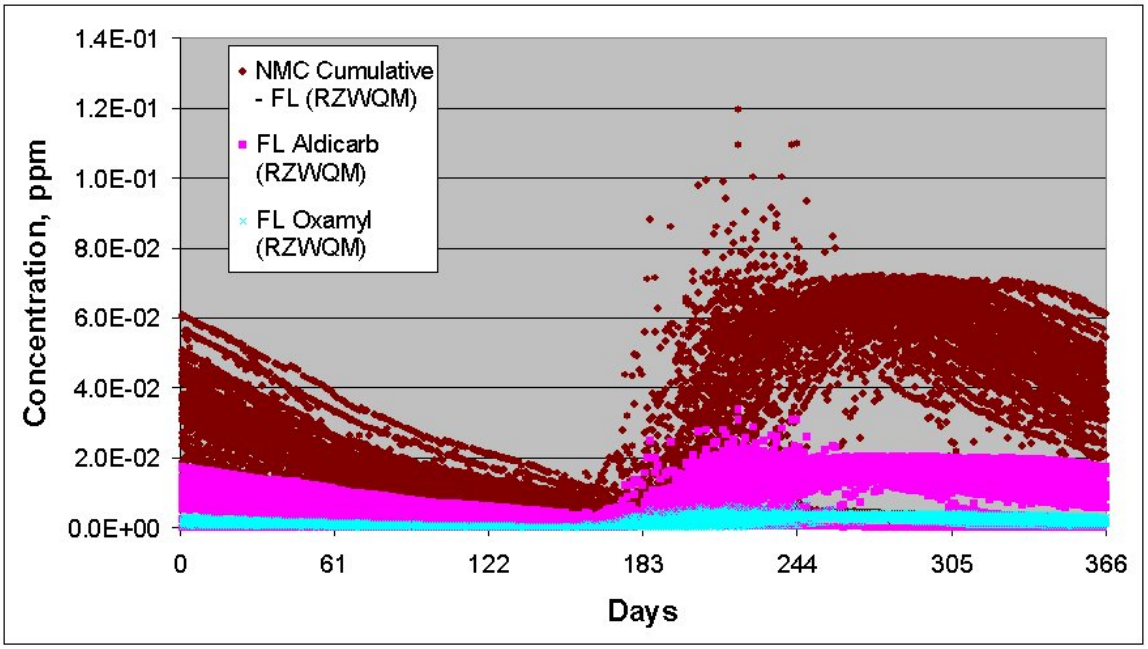
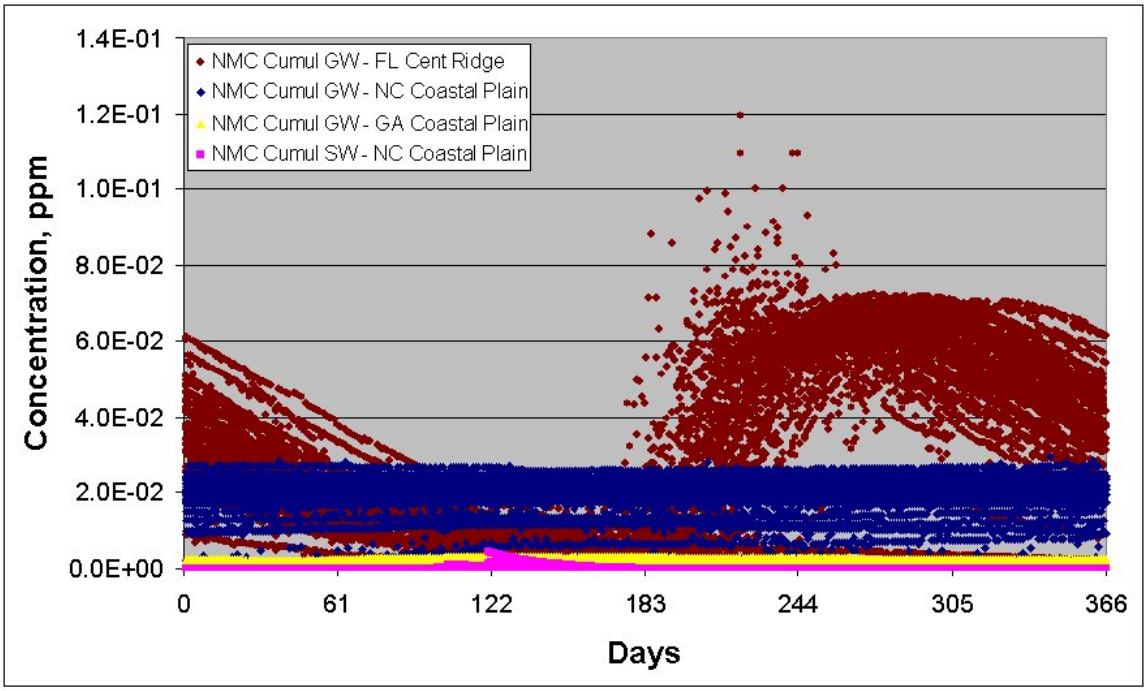


Figure I.D.12. Comparisons of cumulative carbamate exposures in ground water from the FL central ridge (dark red), NC coastal plain (blue), and GA coastal plain (yellow) with the highest surface water exposure (pink) from NC.



I. Preliminary NMC Cumulative Risk Assessment

E. Residential NMC Cumulative Risk

1. Introduction

The EPA's Office of Pesticide Programs (OPP) uses calendar based models (Lifeline, CARES and Calendex™) to assess aggregate or cumulative exposures by incorporating the dietary route with other exposure pathways taking into account the temporal aspects of the residential use of pesticides and the geographic influences of agricultural pesticide use impacting regional drinking water sources.

In nearly all cases, the residential exposure scenarios were developed using proprietary residue and exposure data. Exposure factors such as breathing rates and durations of time spent indoors or outdoors were taken from various sources including OPP's Exposure Factors Handbook (USEPA, 1997). For the majority of residential uses considered in this assessment, the full range of exposure values – expressed as uniform, log-normal, empirical, or cumulative distributions - are used, where appropriate, rather than relying on point estimates. While the dietary and drinking water assessment address only the oral exposure route, the residential assessment considers the dermal and inhalation exposure routes as well as the oral route, which is based on the mouthing behavior of young children.

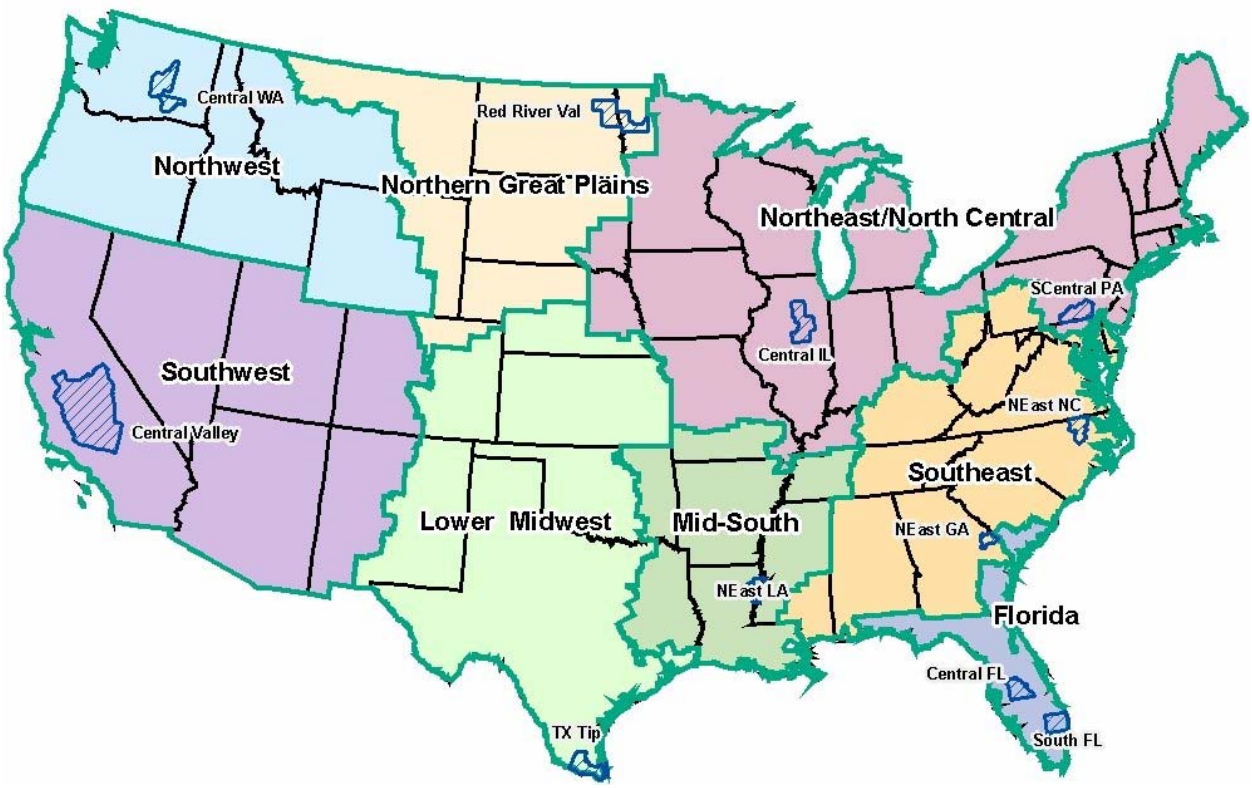
In the preliminary NMC CRA, the temporal aspects of residential pesticide applications were evaluated by relying on information from a variety of sources including registered labels, survey data, and publicly available information provided by State Cooperative Extension Services. These information resources were comprehensively used to identify information such as frequency of applications and the seasonal appearance of target pests. OPP also relied on a national pesticide usage diary survey delineating day of application of registered pesticide products. This longitudinal survey also captures incident of co-occurrence of residential uses of the same pesticide or similar pesticides on the same day. The survey was conducted by the National Family Organization on behalf of the Residential Exposure Joint Venture (REJV). Additional details regarding all use information used in the preliminary NMC CRA is presented in Appendix II.E.1.

2. Scope of Regional Assessments

Three NMC pesticides in this cumulative assessment have residential uses. Carbaryl has registered uses on lawns, fruit trees, vegetable and flower gardens, and ornamental trees and shrubs. Carbaryl also has registrations of impregnated pet collars. Propoxur has registered uses as an indoor crack and crevice spray and impregnated pet collars, and methiocarb may be applied to soil for the control of slugs and snails in and around ornamental plants.

In the preliminary NMC CRA assessment, only the Southern region of the United States was considered. While insect growth may slow during the winter months in the South, unlike other regions of the country, there is no period of dormancy. Since the growing season is longer in the South and the associated pest pressures are therefore greater, this assessment provides a worst case estimate of exposure.

Figure I.E.1 Pesticide Cumulative Assessment Regions



3. Residential Scenarios

The Residential Scenarios addressed in this document represent critical NMC uses that have the potential for significant exposure or risk when considered in a cumulative assessment. A brief description of each scenario is provided below:

a. Lawn Care

Carbaryl (adult applicator and adult and child post application exposure)

Carbaryl may be applied by homeowners or professional lawn care operators (LCO). Granular, dust, and sprayable applications can be made by consumers using push-type spreaders, Ready-to-use shaker cans, and hose-end sprayers respectively. Dermal and inhalation exposure was assessed for homeowners mixing, loading, and applying carbaryl to

residential lawns. This assessment also considered dermal post-application exposure for adults and children contacting treated lawns. Additionally, oral non-dietary exposure (hand-to-mouth) was considered for toddlers transferring treated-turf residues from their hand to their mouth.

Post-application exposure was assessed for the broadcast use of carbaryl and not for the spot treatment uses. OPP is in the process of amending the use pattern of carbaryl. The proposed label changes restrict broadcast lawn application to granular formulations. However, spot treatments with the liquid and dust formulations are permitted. Liquid and dust products will be packaged in ready-to-dispense containers. Such formulations will limit spot treatments to areas of less than 1000 square feet. The current assessment incorporates the proposed label changes for the use of carbaryl on residential lawns.

b. Vegetable Gardens

Carbaryl (adult applicator; adult and teenagers post application exposure)

Dust, liquid, and granular formulations of carbaryl may be applied to garden vegetables using a ready-to-use (RTU) shaker cans, trigger pump sprayers, handwands, trigger pump sprayers or hose-end sprayers. Dermal and inhalation exposure was assessed for homeowners mixing, loading, and applying carbaryl to vegetable garden plants based on data for the liquid and dust formulations. The use of liquid and dust data for granular applications result in higher estimated exposure. Post-application dermal exposure also was considered for adults and teenagers re-entering treated gardens to harvest vegetables or perform maintenance tasks (such as weeding).

c. Ornamentals

Carbaryl (adult applicator exposure; adult and teenager post-application exposure)

Carbaryl may be applied as a dust to ornamental plants using a RTU shaker can. Note that proposed label changes require all home garden products formulated as either a dust or a granular to be packaged in ready-to-dispense containers. Carbaryl may also be sprayed on ornamentals (flowers, trees and shrubs) using a small handwand or hose-end sprayer. The current assessment evaluated exposure for homeowners applying liquid formulations of carbaryl via the handwand sprayer since chemical-specific applicator data suggests that the handwand sprayer resulted in similar yet higher exposure than the hose-end spayer. The data used to assess this scenario accounts for homeowners applying sprays below the waist as well as overhead. Dermal

and inhalation exposure was assessed for homeowners mixing, loading, and applying carbaryl to ornamental garden plants. Post-application dermal exposure also was considered for adults and teenagers performing ornamnental garden maintenance tasks (such as pruning).

Methiocarb (adult applicator exposure)

Methiocarb may be applied to soil areas in and around ornamentals for the control of snails and slugs. This product is formulated as a bait applied as a broadcast application over plant foliage or to the soil surrounding ornamental plants. Exposure from this use is expected to be minimal in comparison to the post-application exposure assessed for the ornamental use of carbaryl. Therefore, post-application exposure was not evaluated for this scenario.

d. Fruit Trees

Carbaryl (adult and teenager applicator and post-application exposure)

Carbaryl may be sprayed to fruit trees using a handwand or hose-end sprayer. The current assessment considers dermal and inhalation exposure for handwand applications only. Chemical specific applicator data for this use indicate greater exposure resulting from handwand applications than from hose-end sprayers, and therefore is considered to be worst case. Post-application dermal exposure was assessed for adults and teenagers harvesting fruit and performing fruit tree maintenance tasks (such as pruning).

e. Indoor Crack and Crevice Sprays

Propoxur (adult applicator; adult and child post application exposure)

Propoxur is registered as a crack and crevice spray. Uses include sprays to cracks, crevices, and small areas inside the home. These types of applications are typically made along baseboards and to small areas behind cabinets and under appliances. For this assessment, it is assumed that professional pest control operators (PCO) may apply spray-able formulations (e.g., wettable powders) while consumers will use hand-held pressurized spray cans. Dermal and inhalation exposure was considered for homeowners applying propoxur as a crack and crevice spray inside the home. Dermal and inhalation post-application exposure was also considered for adults and children living in houses treated with propoxur. Oral non-dietary exposure also was assessed for children who contact indoor surface residues and transfer residues from their hands to their mouths.

f. Pet Collars

Carbaryl (adult and child post application exposure)

Propoxur (adult and child post-application exposure)

Carbaryl and propoxur are formulated as impregnated pet collars. Post-application dermal exposure was considered for adults and children contacting (hugging, petting) treated pets. Oral non-dietary exposure also was assessed for toddlers contacting treated pets and transferring residues from their hands to their mouths.

g. Golf Course

Carbaryl (adult and teenager post-application exposure)

Carbaryl is also used on golf course turf**.** Golf course workers may apply liquid or granular formulations of carbaryl as a broadcast application to fairways, greens and tees. Post-application exposure was assessed for adults and teenagers playing rounds of golf on courses treated with the sprayable formulations of carbaryl.

4. Exposure Routes/Scenarios Considered

The routes of exposure considered in this cumulative assessment varied depending on certain application and post-application exposure activities that were determined to be age group-specific. Since cumulative risk assessments do not include occupational risks, applicator exposure is not assessed for the golf course scenario. However, EPA does perform separate occupational risk assessments for such exposure scenarios. The specific exposure routes and pathways/scenarios are summarized in Table I.E.1 and described in additional detail below:

Table I.E.1 Specific Exposure Routes and Pathways/Scenarios

Scenario	Population	Applicator			Post Application		
		Oral	Dermal	Inhalation	Oral	Dermal	Inhalation
Lawn/Turf	Adults		X	X		X	
	Children 1-2				X	X	
	Children 3-5				X	X	
Home Garden	Adults		X	X		X	
	Youth 13-17					X	
	Children 1-2						
	Children 3-5						
Indoor (c&c)	Adults		X	X		X	X
	Children 1-2				X	X	X
	Children 3-5				X	X	X
Pet Collars	Adults					X	
	Children 1-2				X	X	
	Children 3-5				X	X	
Ornamental Plants and Trees	Adults		X	X		X	
	Youth 13- 17					X	
	Children 1-2						
	Children 3-5						
Fruit Trees	Adults		X	X		X	
	Youth 13-17					X	
	Children 1-2						
	Children 3-5						
Golf Course	Adults					X	
	Youth 13-17					X	

a. Oral Route of Exposure

Toddler ingestion via hand-to-mouth activity was the only oral route of exposure considered in the residential portion of this assessment. Specifically, oral hand-to-mouth ingestion was considered only for children 1-2 and 3-5 years old for the lawn care, crack and crevice, and pet collar scenarios. OPP acknowledges that there are very limited data on exposure to young children; in general, however, children ages six and older no longer exhibit mouthing behavior to the degree seen in younger children. In addition, while OPP recognizes that non-dietary exposure may occur not only from hand-to-mouth activities but also from activities such as ingestion of soil and mouthing of grass, the latter two pathways were not considered because they had little impact on exposure when addressed in the individual chemical risk assessments.

b. Dermal Route of Exposure

The dermal route was assessed for adults applying consumer pesticide products to lawns, gardens, fruit trees, and ornamental plants, as well as indoor surfaces as a crack and crevice spray. For both children and adults, post-application dermal exposure was assessed for the lawn, indoor crack and crevice and pet collar scenarios. The dermal route was also assessed for adults and teenagers reentering treated vegetable and ornamental garden to perform maintenance (weeding, pruning) and harvesting activities. Similarly, exposure was assessed for adults and teenagers involved in fruit tree cultivation. Dermal post-application exposure also was assessed for adults and teens playing golf on treated courses.

c. Inhalation Route of Exposure

The inhalation route of exposure was considered for adults and children. Specifically, inhalation exposure was assessed for adults applying pesticide formulations to lawns, vegetable gardens, ornamental plants and fruit trees, as well as to indoor surfaces as a crack and crevice spray. Post-application inhalation exposure was assessed for adults and children living in households treated with propoxur as a crack and crevice spray.

5. Data Sources

Three basic types of data were considered in this assessment: pesticide use data, residue concentration and dissipation/decay data, and exposure contact factor data. These data are described in more detail below. The potential co-occurrence or mutual exclusivity was not taken into consideration for any combination of residential scenarios assessed for the PNMC CRA.

a. Pesticide Use Data

The probabilistic models require residential pesticide use inputs to aggregate exposure from multiple use scenarios. The percent of households applying the various products, and the timing of those applications directly impact US per capita estimates of aggregate exposure. The REJV data can be used to generate empirically-based estimates to address those needs. Appendix II.E.1 provides further details regarding the REJV data. However, the REJV did not collect information on the purpose of use (pest treated), areas treated, or application rates. Since these factors may impact timing and frequency of application, REJV data was used in combination with professional judgment, product label information and pest pressure information from the Cooperative State Extension Services. The PNMC CRA considered only the South Region of the United States because the growing season is longer in the South and the associated pest pressures are therefore greater. Since water concentrations are highest in Florida, all pesticide use data was based on pest pressures in Florida. Pest pressure data for Florida is assumed to conservatively address pest pressure for other area of the country where NMC water concentrations are high, (such as North Carolina). Due to longer periods of pesticide use coupled with higher NMC ground water concentrations, this assessment is assumed to provide a worst case estimate of exposure.

The preliminary assessment focuses on post-application exposures for children, including the broadcast lawn, the pet collar, and the crack and crevice scenarios. Examples of how pesticide use data was incorporated into these scenarios are discussed below.

i. Broadcast Lawn Scenarios

Current label revisions for carbaryl lawn care products restrict broadcast applications to granular formulations. Therefore, post-application exposure for children was assessed only for granular applications of carbaryl to lawns. The major turf pests treated with carbaryl are grubs, mole crickets, caterpillars, cinch bugs, scales, ticks, and a variety of spiders, and ants. However, pests that would mostly likely be treated with granular applications are mole crickets and white grubs. The other pests listed are more likely to be treated with spray applications. Therefore, this assessment

focused on timing of applications for residential lawns treated for white grubs and mole crickets. Information from the University of Florida Cooperative State Extension Service indicates that grubs actively feeding in Florida from April through October, depending on species and weather conditions. Additionally, tawny mole crickets become active in March, and granular is typically used in August and September. For these reasons, the broadcast lawn assessment considered the season of use to be early spring through fall. OPP used the maximum application rate, as allowed by currently registered labels, to assess exposure.

ii. Pet Collar Scenarios

Propoxur and carbaryl product labels indicate that pet collars are effective for 180 days and 120 days, respectively. Additionally, season of use is considered to be year-round since flea lifecycle information shows that in humid climates, fleas may be active year-round. Therefore, the pet collar assessment assumed that application of pet collars would be made two times per year. OPP used the maximum application rate, as allowed by currently registered labels, to assess exposure.

iii. Indoor Crack and Crevice Scenarios

Propoxur crack and crevice products are used to treat nuisance pests (ants, roaches, etc.) and instruct consumers to re-treat as necessary. Use of these types of products, especially in southern climates where there is no period of insect dormancy, is therefore expected to be year-round. For the PNMC CRA, applications of the propoxur indoor treatments were assumed to occur at any time of the year, with multiple re-treatments possible. OPP used the maximum application rate, as allowed by currently registered labels, to assess exposure.

b. Residue Concentration Data

Residue concentration data and associated pesticide decay/dissipation parameters were used to define the sources and magnitude of exposure resulting from human contact with transferable residues. In many cases, chemical-specific data were used to assess homeowner applicator and post-application exposure resulting from the registered uses of carbaryl. For the lawn and garden scenarios, data from the *Outdoor Residential Pesticide Use and Usage Survey and National Gardening Association Survey* (Johnson, 1999) submitted by Outdoor Residential Exposure Task Force (ORETF) were also used. Chemical-specific data also were used to assess indoor exposure for adults and children living in households treated with propoxur. Surrogate data was used to determine exposure resulting from the ornamental garden use of

methiocarb. Appendix II.E.2 contains a summary all residue data used in the preliminary NMC CRA, as well as the derivation of various distributional parameters.

c. Exposure Factor (Contact) Data

Exposure factors such as the amount of time spent in an area, frequency of hand-to-mouth contacts, size of area treated, and location of residue source (lawn, garden, or indoor surface) are critical for estimating exposures to a given substance. Appendix II.E.2 contains a summary all exposure factors used in the preliminary NMC CRA, as well as the derivation of various distributional parameters. Unless otherwise noted, all distributions were truncated at the 99th percentile in order to avoid a distribution which contained values that were well beyond those deemed reasonable.

6. Exposure Scenarios

This assessment considered a variety of exposure scenarios for consumer applicator and post-application exposures. Each of these is described in additional detail below. Since it is difficult to determine typical rates for homeowner products, OPP used the maximum application rate, as allowed by currently registered labels, to assess exposure for all scenarios. (8 lbs al/A was used for lawns and fruit trees; and 2 lbs ai/A was used for vegetable gardens and ornamentals).

a. Lawn Care Exposure Scenarios

i. Lawn Applicator Exposure

Only carbaryl has registered lawn care uses. Applicator exposure was assessed for homeowners mixing, loading and applying a variety of carbaryl products to their lawns. There are three formulations of carbaryl that are available for lawn use: granular, dust, and liquid sprayable formulations. OPP is in the process of amending the use pattern of carbaryl and the current cumulative assessment incorporates these changes. The proposed label changes restrict broadcast lawn application to granular formulations. However, spot treatments of the liquid and dust formulations are permitted. Liquid and dust products will be packaged in ready-to-dispense containers. Such formulations will limit spot treatments to areas of less than 1000 square feet.

Total exposure is calculated as the product of the unit exposure (UE) (either dermal or inhalation), the application rate, and the lawn size.

Unit Exposures: Both dermal and inhalation exposure routes were considered. ORETF studies were used for the granular broadcast and liquid spot treatment scenarios.

The ORETF (Outdoor Residential Exposure Task Force) submitted a report (Klonne, 1999) in which a variety of products were used on turf. In these studies, both homeowners and lawn care operators (LCOs) were monitored following broadcast applications to turf. All of the data submitted in this report were completed in a series of studies.

The two studies that monitored homeowner exposure resulting from granular spreader (Klonne, 1999/OMA003 Study) and hose-end sprayer (Klonne, 1999/OMA004 Study) applications were used in this assessment. Volunteers participating in these exposures studies were adult non-professionals who use pesticides on their own gardens and lawns. Many of the volunteers selected as subjects in these studies were members of garden clubs. All volunteers made their applications without specific instruction from the study investigators. Unit exposures estimated from these studies cover various clothing scenarios that range from wearing short pants and short sleeved shirts, to long pants and long sleeved shirts.

Applicator exposure for homeowners applying dust formulations of carbaryl as a spot treatment to residential turf was assessed using carbaryl data for dust applications in gardens (Mester, 1998a). This data is considered the best available to assess applicator exposure for this use.

All dermal and inhalation unit exposure were normalized and expressed as milligrams exposure per pound of active ingredient handled (mg/lb ai) (referred to as unit exposures, or UE). The lognormal distributions of the UEs for the lawn applicator scenarios are shown in

Table I.E.2.

Table I.E.2 Lognormal Distributions of Unit Exposures Used for Carbaryl Lawn Care Scenarios

Application Method	Exposure Route	Unit Exposure Distribution (mg/lb ai)	Comments
Granular Rotary Spreader	Dermal	LN(0.81, 0.57)	This distribution was used for the broadcast lawn scenario
	Inhalation	LN(0.0013, 0.0013)	
Dust Shaker/Powder	Dermal	LN(250, 330)	This distribution was used for the SPOT treatment on lawns. This distribution was also used for vegetable garden and ornamental scenarios
	Inhalation	LN(2.9, 9.5)	
Hose-end Sprayer on Turf	Dermal	LN(8.4, 26)	This distribution was used for the lawn SPOT treatment scenario ONLY
	Inhalation	LN(0.022, 0.040)	

NOTES:
- ❑ LN(μ, σ) represents a lognormal distribution with μ = mean and σ = standard deviation.
- ❑ For lawn scenarios, information was derived from carbaryl-specific data and studies conducted by the ORETF (Outdoor Residential Exposure Task).
- ❑ A more detailed explanation of the statistical analysis of this data is provided in Appendix II.E.2.

Application Rates: For all scenarios assessed, OPP used the maximum application rate to assess exposure (8 lbs ai/A was used for the lawn care scenario).

Area Treated: An important variable for estimating home-owner applicator exposure is the size of the lawn. OPP considered the average and median lawn sizes reported in a journal article by Vinlove and Torla (1995). The means and medians were ~13,000 ft^2. However, the authors noted problems interpreting the data since it is based primarily on low income houses and consists of adjustments of the lot size by the house's foundation (footprint) only. The data do not consider other structures such as decks or other green space such as gardens, which can reportedly reduce the lot size by up to 50%. Similar lawn sizes were noted in ORETF study (Johnson, 1999) with similar problems encountered with respect to confounding variables such as decks and other green spaces. For this assessment, OPP used a uniform distribution for lawn size bounded by 1000 ft^2 and 20,000 ft^2. The lower end of this range considers smaller lawns for residences such as town houses. The upper bound of 20,000 ft^2 (~ ½ acre) appears reasonable given the type of application equipment assumed to be used by residential applicators. Information from the ORETF survey also indicates that many pesticide users make spot treatments of insecticides. Similarly for spot treatments, OPP assumed a uniform distribution for treated area bounded by 100 ft^2 and 1000 ft^2.

ii. Lawn Post-Application Dermal Exposure

The fate of pesticides applied to turf, and subsequent human contact, is a key variable for assessing post-application dermal exposure and can be an important exposure pathway to consider as part of a cumulative assessment. This exposure pathway was evaluated here in the preliminary NMC Cumulative Risk Assessment by using data from a number of available studies (described in more detail below). Briefly, post-application dermal exposure (mg pesticide) is calculated by multiplying the residue concentration on the lawn (mg/cm^2) by the transfer coefficient (cm^2/hour) derived from literature and other studies and the time spent on the lawn (hours/day). For this assessment, the transfer coefficient and the time spent on lawns were represented by a distribution of values while the residue concentration on the lawn was represented by a time series of concentration values (which accounted for residue degradation over time and incorporated the relevant half-lives or decay coefficients). Due to the proposed label revisions, post-application exposure was considered for the granular broadcast treatments only.

Residue Data: There are no chemical-specific turf transferable residue (TTR) data for granular formulations of carbaryl. However, there are TTR data for liquid formulations of carbaryl (Mester, 1999). The liquid TTR data is available for three sites. At each site, 3 replicate samples were taken for 14 days following two applications of carbaryl. The liquid TTR data from the site (Georgia) resulting in the highest residue values was used. The use of liquid TTR will result in higher exposure than that of granular and therefore provides a conservative assessment of risk resulting from the lawn uses of carbaryl. This assessment assumes an initial concentration of 0.00065 mg/cm^2. Dissipation is based on a 3.6 day half-life, with residues set to zero 14 days after application. Although the carbaryl TTR studies show low but detectable residues for samples taken 14 days after application, it is assumed that lawn care maintenance practices (such as mowing, or watering) will remove residues from turfgrass within 2 week of application.

Transfer Coefficients (TC): The transfer coefficients used in this assessment were developed by dividing the hourly dermal exposure (µg/hour), (obtained from a set of activities in the dermal exposure studies), by the measurement commonly referred to as turf transferable residues (TTR) (µg/cm^2). Deposition estimates (ai per acre) were assumed to have a TTR transfer efficiency of 1 percent. This corresponds to the transfer efficiency of 1.2 percent observed in the carbaryl TTR dissipation study (Mester, 1999). Transfer efficiency is derived by dividing the measured TTR

($\mu g/cm^2$) by deposition ($\mu g/cm2$) times 100. Again, since none of the dermal exposure studies used to estimate hourly exposure in the above chemical specific residue studies permitted direct calculation of the TTR, the transfer coefficients used in this assessment were developed by assuming a transfer efficiency of one percent for spray formulations. This approach was taken for two reasons:

- To make use of available dermal exposure measurements in the above studies which are not influenced by TTR method, and
- To make use of the available residue dissipation data for which there are no corresponding dermal exposure transfer coefficients

A more detailed discussion of the relationship of transfer coefficients and TTRs can be found in "Overview of Issues Related to the Standard Operating Procedures for Residential Exposure Assessment" presented to the FIFRA Scientific Advisory Panel (USEPA, 1999d).

Using the above-indicated calculation methodology, exposure studies were used to derive TCs for individuals reentering treated lawns. Separate studies are available and used for children and adults. These studies are described in additional detail below.

As indicated in the previous section, the lawn care assessment relied upon liquid TTR data instead of granular TTR data. Since liquid TTR data were used, liquid TCs were also used in this assessment. This approach provides a conservative assessment of risk for the lawn uses of carbaryl because using liquid data as a surrogate for the granular broadcast scenario will result in higher estimated exposure.

Transfer Coefficients used to assess children's exposure to treated lawns: A study by Black (1993), which investigated dermal exposure values of young children who were exposed to a non-toxic substance, was used to estimate exposure contact factors for children contacting treated lawns. In this study, children performed unscripted activities on turf treated with a non-toxic substance used as a whitening agent in fabrics. The subjects of the study were 14 children aged four to nine years old. In this study, children were provided toys and their activities were recorded as they performed unscripted activities for a period of one half hour. Activities recorded were grouped into the following classifications:

- ❑ Upright (standing, walking, jumping and running)
- ❑ Sitting (straight-up, cross legged, kneeling, crouching and crawling)
- ❑ Lying (prone or supine)

Dermal exposure was measured by fluorescent measurement technology described in Fenske et al., (1986). Measurements on various body parts were expressed as ug/body part (e.g., hand, face, etc.) and as concentration (ug/cm^2).

In a second study (Vaccaro, 1993) in which a liquid formulation was used, eight adults performed structured activities intended to mimic a child's activities (including walking/running, sleeping, crawling, and sitting on turf).

The subjects performed these activities for a period of four hours beginning four hours after the turf had dried. Turf had been treated earlier with a sprayable form of chlorpyrifos and exposure was estimated in the study by monitoring the amount of a chlorpyrifos metabolite – excreted over the following period of 6 days. This method directly measured internal dose and was used to back-calculate a generic "to the skin" transfer coefficient by using chemical specific dermal absorption data for chlorpyrifos (Nolan et al., 1984).

These concentrations were normalized to represent the surface area of children three to four years of age for use with a standardized body weight of 15 kg. Standard surface area values were taken from the Agency's Exposure Factors Handbook (EFH), (USEPA 1997). The transfer coefficients used in this assessment were estimated from this study.

For children's dermal post-application exposures to treated lawns, the NMC cumulative assessment used a lognormal distribution of transfer coefficients from Black (1993) and Vaccaro (1993) noted above. The lognormal distribution is represented by a mean of 5700 cm^2/hour and a standard deviation of 3600 cm^2/hour. The lognormal distribution was truncated at the calculated 99th percentile of the distribution (i.e.,18700 cm^2/hour for the spray application) This was done in order to avoid a distribution which contained values that were well beyond those deemed reasonable.

Transfer Coefficients used to assess adult exposure to treated turf: The Vaccaro (1993) study detailed above also was used to estimate TCs for adults.

For adult post-application dermal exposures to treated lawns, the NMC cumulative assessment used a distribution of transfer coefficient characterized by a lognormal distribution with a mean of 9,400 cm^2/hour and a standard deviation of 4500 cm^2/hour for the spray application. The lognormal distribution was truncated at the calculated 99th percentile of the distribution (i.e. 25000 cm^2/hour).

Duration: Another important variable for addressing post-application exposure from home lawn treatment is the duration of time spent on lawns. In this NMC CRA, cumulative distributions of durations on lawns of up to two hours were used to address adult exposure on lawns. These data are presented in Table 15-64 of the EFH (USEPA, 1997); however, OPP notes that the percentiles above the 95th have the same values (121 minutes). A similar cumulative distribution was given for children ages one to five. In order to be protective of children and to address the uncertainty in the upper percentiles of the exposure factor data, OPP selected an empirical distribution (which was expressed as a cumulative distribution function) from the EFH's Table 15-80 with a bound of 3.5 hours for children. This distribution represents the amount of time spent outdoors rather than just on lawns. This adjustment allows for additional time that children may spend outdoors (such as parks and schools) where there is potential for additional contact with treated turf.

iii. Lawn Non-Dietary Hand-to-Mouth Exposure

The assessment also incorporates exposure resulting from toddler hand-to-mouth activity on lawns. Briefly, exposure through this pathway is calculated as the product of the following factors: residue concentration (mg/cm^2), hand-to-mouth contact frequency ($hour^{-1}$), surface area of inserted hand parts (cm^2), saliva extraction efficiency (unitless), wet hand adjustment factor (unitless), and hours spent on lawn (empirical distribution). Implicit in all hand to mouth exposure estimates, is the constant replenishment of residues on the hands between each mouthing event. This assumption may overestimate exposure when coupled with upper percentile factors such as percent of hand mouthed and frequency of events. These factors are fixed throughout the exposure calculation for a given individual.

Residue Data: The TTR data (Mester, 1999) used to estimate hand-to-mouth exposure is the same as that used to estimate dermal post-application exposure for residential turfgrass.

Frequency of Mouthing Behavior: For the preliminary NMC CRA assessment, the frequency of hand-to-mouth events is based on

Zartarian, 2003 (SRA presentation). The estimates of mouthing frequency were derived from several exposure studies and videotaping studies. Statistical analysis indicated that a Weibull distribution best fit the data. For the lawn care scenario, hand-to-mouth events per hour were based on outdoor frequencies as defined by a Weibull distribution (mean = 7 events/hour, standard deviation = 12). OPP is aware of additional data addressing this factor and will consider it upon further analysis and availability in the published literature. The Agency is in the process of updating the Child-Specific Exposure Factors Handbook (USEPA, 2002c). In the interim, OPP believes that the presentation cited above provides the best available data to assess children's hand-to-mouth exposures.

Surface Area of Hand Mouthed (cm^2): The preliminary NMC CRA relied on Zartarian's (2003) analysis of surface area of hand mouthed. The analysis used the same studies as those used to assess frequency of mouthing events (as listed above) to determine the fraction of the hand mouthed. The fraction of hand mouthed values were fit with a beta distribution. To determine the surface area mouthed, fraction of hand mouthed values from the fitted beta distribution weremultiplied by the palmar surface area of the hand (200 cm^2).

Saliva Extraction Factor: To address the removal of residues from the hands by saliva during mouthing events, several studies were considered. The removal efficiency of residues on hands by saliva and other substances (e.g., ethanol) suggests a range of removal efficiencies (Geno et al., 1995; Fenske and Lu 1994; Wester and Maibach 1989). Based on the above studies, a uniform distribution of 20% to 50% was used in this assessment for saliva extraction factors.

Wet Hand Adjustment Factor: Hands wet from saliva are reportedly more efficient at residue transfer than dry hands. A uniform distribution of transfer efficiency multipliers of 1.5 to three times was selected to address the increased efficiency of wet hands. The increased efficiency is based on comparisons of wet vs. dry hands when pressed onto treated carpets and vinyl tiles described by Clothier (1999a and 1999b). The TTR methods used in the Clothier studies had similar efficiencies as the chemical specific lawn residue data (TTR data) used in this assessment.

Duration: The time spent on the lawn was estimated as a cumulative distribution ranging from 0 hours to 3.5 hours. To be protective of childrens' exposure and to address the uncertainty of the upper percentiles of the exposure factor data, OPP selected a cumulative distribution from EFH (USEPA, 1997) Table 15-80 with

a bound of 3.5 hours for children 1 to 5 years old. This distribution represents the amount of time spent outdoors. This allows for the time that children spend outdoors not only at home but also in parks and near schools.

Assessing exposure through the non-dietary ingestion pathway is difficult due, in part, to issues associated with measurement of the above-discussed variables as well as issues associated with the utility of using children's hand-to-mouth frequencies based on indoor activities for outdoor exposure scenarios. There are also differences in mouthing behavior based on active and quiet play with increased mouthing likely to be during activities of quiet play. Limited data evaluated by Groot et al., 1998 suggests that children aged six to 12 months (exceeding 160 minutes per day) can experience longer durations of mouthing activities than children 18 to 36 months (up to 30 minutes per day). However, children in this age group are not likely to be engaged in post application lawn activities OPP is modeling that would result in higher estimated exposure. Additional data for very young children (under the age of two) are needed to delineate the frequency differences between hand-to-mouth events for children engaged in active and quiet play.

b. Vegetable Garden Exposure Scenarios

Carbaryl has registered uses in home vegetable gardens. This assessment includes scenarios for applications of carbaryl using dust formulations (hand/shake), ready-to-use trigger sprayers, and hose-end sprayers. While there are other possible application methods for use on these sites, these application methods were selected based on use and exposure considerations.

i. Applicator Exposure

Dermal and inhalation exposures for homeowners applying carbaryl to their vegetable gardens were calculated in a manner similar to that used to assess applicator exposure for the lawn care scenario. Both are the product of the unit exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2).

Unit Exposure: Dermal and inhalation unit exposures were derived from chemical-specific data (Mester, 1998a) for dust (shake/pour), trigger pump sprayer, and liquid hose-end sprayer applications to vegetable gardens. The UE for all garden scenarios are based on lognormal distribution as listed in Table I.E.3.

Application Rate: An application rate of 2 lbs ai/A was used for all vegetable garden scenarios. This corresponds to the maximum

label application rate for liquid applications to garden sites. Application rates for the trigger pump sprayer and dust formulations are considerably lower than 2 lbs ai/A. This assessment conservatively uses the 2 lb ai/A application rate for these scenarios as well.

Area Treated: For vegetable gardens, the area treated was entered as a lognormal distribution (mean = 4600 ft^2, standard deviation =1500 ft^2, and maximum = 8000 ft^2); these dimensions are based on data from the National Home and Garden Pesticide Use Survey (USEPA, 1992). In these assessments, it is assumed that the entire garden is treated. Home gardens consist of many types of vegetables which may not all need to be treated since they tend to have different pest pressures (e.g. squash vine borer and corn earworm may not appear at the same time).

Table I.E.3. Lognormal Distributions of Unit Exposures Used for Carbaryl Garden, Fruit Tree, and Ornamental Scenarios

Application Method	Exposure Route	Unit Exposure Distribution (mg/lb ai)	Comments
Hose-End Sprayer	Dermal	(51, 58)	This distribution used for the vegetable garden scenario ONLY
	Inhalation	(0.0024, 0.0015)	
Liquid Handwand	Dermal	(74, 64)	This distribution also used for the ornamental and fruit tree scenarios
	Inhalation	(0.009, 0.010)	
Dust Shaker/Powder	Dermal	(250, 330)	This distribution was used for vegetable garden and ornamental scenarios. This distribution was also used for the SPOT treatment on lawns.
	Inhalation	(2.9, 9.5)	
RTU trigger pump sprayer	Dermal	(86, 110)	This distribution was used for the vegetable garden and ornamental scenarios.
	Inhalation	(0.10, 0.14)	

NOTES:
- ❑ LN(μ, σ) represents a lognormal distribution with μ = mean and σ = standard deviation
- ❑ Studies for garden, fruit tree, and ornamental applications are carbaryl-specific.
- ❑ A more detailed explanation of the statistical analysis of this data is provided in Appendix II.E.2.

ii. Post-Application Dermal Exposure

Post-application exposure for adults and teenagers harvesting vegetables or performing post application gardens maintenance were assessed using a range of transfer coefficients to account for the diversity of activities. Post application exposure was estimated as the product of dislodgeable residue concentration (mg/cm^2) a transfer coefficient (cm^2/hour), and time spent in the activity (hours).

Residue Data: Chemical-specific dislodgeable foliar residue data on sunflowers (Klonne et al, 1999) was used to assess dermal post-application exposure. Although OPP has additional information regarding carbaryl specific DFR data on cabbage (Klonne et al, 2000a) , the sunflower DFR data was used since the residues detected in the sunflower study were higher than those detected in the cabbage study. Statistical analysis of the carbaryl sunflower DFR data was performed. The initial residue concentrations and the half-life were determined to be 0.0061mg/cm^2 and 5 days, respectively.

Transfer Coefficient: For the vegetable garden scenario, transfer coefficients were characterized by a uniform distribution ranging from 180 to 1000 cm^2/hour, to reflect a range of gardening tasks for a variety of crops of differing heights and foliage development. The TCs used in this assessment were derived from studies on chrysanthemum pinching (Rotondaro, 2000) and cabbage weeding

(Klonne et al, 2000a). All transfer coefficients are based on individuals wearing short sleeved shirts and short pants. A reduction factor was applied to account for body weights and surface area differences between adults and teenagers.

Duration: The time spent harvesting or performing post-application maintenance activities was represented by a uniform distribution ranging from 0.17 hour/day to 1 hour/day. These estimates of time spent in the garden performing post application activities (as well as the frequency of applications) were based on the ORETF survey (Johnson et al, 1999).

c. Ornamental Plants and Shrubs Exposure Scenarios

Carbaryl also has registered uses on ornamental plants and shrubs. This assessment includes scenarios for the RTU dust formulations, RTU trigger pump sprayers, and liquid hand wand uses on ornamental plants. While there are other possible application methods for use on this site, these methods were selected based on use and exposure considerations.

i. Applicator Exposure

Dermal and inhalation exposures for homeowners treating ornamental plants were estimated as the product of the Unit Exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2).

Unit Exposure: Dermal and inhalation unit exposures were derived from chemical-specific data for carbaryl used on ornamental plants (Mester, 1998a; Merricks, 1998). The UE for all garden scenarios are based on lognormal distribution as listed in Table I.E.3.

Application Rate: An application rate of 2 lbs ai/A was used for all ornamental garden scenarios. This corresponds to the maximum label application rate for liquid applications to garden sites. Application rates for the trigger pump sprayer and dust formulations are considerably lower than 2 lbs ai/A. This assessment conservatively uses the 2 lbs ai/A application rate for these scenarios as well.

Area Treated: The area treated was entered as a uniform distribution of 500 to 2000 ft^2; these dimensions are based on data from the National Home and Garden Pesticide Use Survey (USEPA, 1992) and professional judgement. The ornamental bed size was determined by estimating the perimeter of 2200 ft^2 house.

It is assumed that the majority of ornamental beds are located around the perimeter of the house.

ii. Post-Application Dermal Exposure

Post-application exposure for adults and teenagers performing ornamental garden activities were assessed using a range of transfer coefficients to account for the diversity of activities. Post application exposure was estimated as the product of dislodgeable residue concentration (mg/cm^2), transfer coefficient (cm^2/hour), and time spent in the activity (hours).

Residue Data: Chemical-specific dislodgeable foliar residue data on sunflowers (Klonne et al, 1999) was used to assess dermal post-application exposure from harvesting or performing maintenance activities in ornamental gardens. Although OPP has additional information regarding carbaryl specific DFR data on cabbage (Klonne et al, 2000a) , the sunflower DFR data was used since the residues detected in the sunflower study were higher than those detected in the cabbage study. A statistical analysis of this data was performed and the initial concentration was estimated to be 0.0061 mg/cm2. Residue dissipation is based on the half-life of 5 days. The half-life used in this assessment was determined from the statistical analysis of the carbaryl sunflower DFR data.

Transfer Coefficient: For the ornamental garden scenario, a uniform distribution of transfer coefficients, ranging from 99 to 550 cm^2/hour, was used to reflect a range of gardening tasks. The TCs used in this assessment were derived from studies that evaluated chrysanthemum pinching (Rotondaro, 2000) and nursery stock pruning (Klonne et al, 2000b). All transfer coefficients are based on individuals wearing short sleeved shirts and short pants. A reduction factor was applied to account for body weights and surface area differences between adults and teenagers.

Duration: The time spent harvesting or performing post-application maintenance activities was represented by a uniform distribution ranging from 0.17 hour/day to 1 hour/day. These estimates of time spent in the garden performing post application activities (as well as the frequency of applications) were based on the ORETF survey (Johnson et al, 1999).

d. Fruit Tree Exposure Scenarios

Carbaryl also has registered uses on fruit trees. This assessment addresses exposure for homeowners applying sprayable formulations of carbaryl via handwands. While there are other possible application

methods for use on these sites, this method was selected based on use and exposure considerations.

i. Applicator Exposure

As described for the lawn applicator scenario, exposure is the product of the unit exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2).

Unit Exposure: The dermal and inhalation unit exposures were derived from chemical-specific data for liquid handwandapplications to fruit trees (Merricks, 1998). These unit exposures are based on study data in which applications were made with handwands, spraying below the waist as well as overhead. The UEs for fruit tree scenario are based on lognormal distribution as listed in Table I.E.3.

Application Rate: For all scenarios assessed, OPP used the maximum application rate to assess exposure (8 lbs ai/A was used for the fruit tree scenario).

Area Treated: For fruit trees, most of which are of the dwarf variety and therefore occupy relatively small areas, the area treated was entered as a uniform distribution (minimum 500 ft^2, maximum 2000 ft^2). This distribution was used because specific data is not available on the area covered by home garden fruit trees on the average homeowner's property.

ii. Post-Application Dermal Exposure

Dermal post-application exposure for adults and teenagers harvesting or pruning fruit trees was assessed using TCs from an apple pruning study. Post application exposure was estimated as the product of dislodgeable residue concentration (mg/cm^2), transfer coefficient (cm^2/hour), and time spent in the activity (hours).

Residue Data: Chemical specific dislodgeable foliar residue data on olive trees (Klonne et al, 2000c) was used to assess dermal post-application exposure for this scenario. Statistical analysis of this data was performed and the initial residue concentrations were determined to be 0.0035 mg/cm^2. Residue dissipation is based on the half-life of 7 days (as determined by the statistical analysis of the carbaryl olive DFR data).

Transfer Coefficient: For the fruit tree scenario, the distribution of transfer coefficient was characterized as lognormal, with a mean of 940 cm^2/hour and a standard deviation of 260 cm^2/hour. The TCs were based on an apple pruning study. All transfer coefficients are

based on individuals wearing short sleeved shirts and short pants. A reduction factor was applied to account for body weights and surface area differences between adults and teenagers.

Duration: The time spent harvesting or performing post-application maintenance activities was represented by a uniform distribution ranging from 0.17 hour/day to 1 hour/day. These estimates of time spent in the garden performing post application activities (as well as the frequency of applications) were based on the ORETF survey (Johnson et al, 1999).

e. Ornamental Garden - Snail and Slug Bait Scenarios

This assessment includes the bait use of methiocarb in ornamental gardens. Applicator exposure is calculated as the product of the unit exposure (mg/lb ai handled), application rate (lbs ai/ft^2), and area treated (ft^2).

i. Applicator Exposure

Unit Exposure: The dermal and inhalation UEs for the methiocarb snail and slug bait scenario were based on study data for disolfoton applications to residential shrubs and flower beds (Merricks, 2001). The surrogate data consist of dermal and inhalation measurements of individuals using granular products. Specifically, the field study was conducted in Vero Beach, Florida. A total of 15 volunteers were monitored using passive dosimetry (hand/forearm wash solutions and personal air monitors). Application of the product was made by pouring the granules into the measuring cup/lid attached to the product package, and then distributing the granules onto the soil around the base of a shrub or onto a flower bed. The granules were then soil-incorporated with a garden rake. Each volunteer applied granular disulfoton around shrubs while wearing gloves and then again without gloves. Exposure data from the 30 replicates who did not wear gloves were reported. A lognormal distribution with a mean of 0.23 mg/lb ai, a standard deviation of 5.8 mg/lb ai, and maximum value of 3.4 mg/lb ai (representing the estimated 99th percentile of the lognormal distribution) was used to assess dermal exposure. A single point estimate of 0.00001 mg/lb ai (1/2 LOQ) was used for the inhalation UE since all measured values for inhalation were non-detects.

Application Rate: The application rate used in this assessment is based on the maximum label application rate of 0.2 lbs ai/1000 ft^2.

Area Treated: The area treated was entered as a uniform distribution of 10 to 2000 ft^2; these dimensions are based on data from the National Home and Garden Pesticide Use Survey

(USEPA, 1992) and professional judgement. The low value of 10 sq ft was based on the label direction for treating small areas. The high value for ornamental bed size was determined by estimating the perimeter of 2200 ft^2 house. It is assumed that the majority of ornamental beds are located around the perimeter of the house.

ii. Post-Application Exposure

Since this product is formulated as a bait applied as a broadcast application over plant foliage or to the soil surrounding ornamental plants, post-application exposure is expected to be minimal in comparison to the post-application exposure assessed for the ornamental use of carbaryl. Therefore, post-application exposure was not evaluated for the methiocarb snail and slug bait scenario.

f. Indoor Crack and Crevice Scenarios

The only NMC registered for indoor use is propoxur. Chemical specific data are available to assess its use as an indoor crack and crevice treatment applied (for the purposes of this assessment) as either a pressurized spray (aerosol) by consumers, or as a liquid spray by licensed pesticide control operators (PCO).

i. Applicator Exposure

For this assessment, adult applicator exposures via the dermal and inhalation routes were developed for individuals using the pressurized formula of propoxur. Dermal and inhalation applicator exposure is estimated as the product of unit exposure (mg/ounce ai handled) and the application rate (ounces of ai applied/day.

Unit Exposure: Dermal and inhalation UEs were derived from chemical-specific study data (Knarr, 1988a). Specifically, applicators in the study each applied one 16-ounce aerosol can in each of the 15 residences situated in Vero Beach, Florida. The entire contents were applied to each house. The volunteers sprayed to cracks, crevices along baseboards and other woodwork, under sinks and behind appliances. The majority of the exposure was to the hands, neck and head (~85%). The highest replicate values for both dermal and inhalation UEs were used in this assessment. (25 and 0.23 mg/ounce handled, respectively).

Application Rate: For this preliminary assessment, homeowners were assumed to apply between 10% and 50% (uniform distribution) of a 16 ounce aerosol can (0.5% ai) during a single

event; this was represented by a uniform distribution for total amount (ai) applied (0.008 to 0.04 ounces applied/day).

ii. Post-Application Dermal Exposure

There were limited data to assess post-application exposure for this use. Dermal post-application exposure (to adults and children) was calculated as the product of residue concentration (mg/cm^2), the transfer coefficient (in cm^2/hour), and the duration of exposure (hours/day). A further description of each of these terms is presented below:

Deposition Data: Chemical specific deposition data (Knarr, 1988b) was used for this assessment. Residue data were collected as wipe samples (using OSHA wipe method) and total deposition for 5 intervals following a crack and crevice spray treatment to homes in the vicinity of Kansas City, Missouri. The wipe samples showed no discernable decay pattern over the 48 hour sampling period. This was likely due to the wide variety of sample locations in relation to the area treated with spray. The house was unoccupied during the sampling period. To provide a conservative assessment of risk, this assessment used only total deposition measurements taken in the kitchen and bathroom for exposure assessments covering the entire time spent in the household. OPP assumes a higher residue removal efficiency for hard surfaces versus carpets/upholstery. Therefore, the average values from the hardwood samples are used in both the non-dietary assessment and the dermal assessment for this scenario. A lognormal distribution, with a mean of 0.001 mg/cm^2 and standard deviation of 0.019 mg/cm^2, was used to assess dermal exposure resulting from the crack and crevice use of propoxur.

Dissipation for dermal exposure was calculated based on the assumption of 10 % dissipation per day with residue values set to "0" after 7 days. Dissipation of chemicals indoors is likely to be impacted by several factors and confounded by others. First, the chemical is applied to areas that are less likely to be contacted and may be found in varying concentrations based on house's configuration and flooring materials. While dissipation may be slower indoors than outdoors because of the obvious environmental factors, other factors such as cleaning, dusting and vacuuming may have a greater impact. Also indoor sinks such as carpet backing and polyurethane foam upholstering may also play a role. Any sense of removal of residues via the activity patterns of the residents in the houses used in the study cannot be determined as the houses were unoccupied. Also due to the short sample time, the impact of air exchange rates for the housed cannot be evaluated.

Transfer Coefficient: Transfer coefficients were specified as point estimates for adults (16700 cm^2/hour) and for children ages 1-12 (6000 cm^2/hour). Estimating post application exposures resulting from the crack and crevice use is difficult due to the variability of the residue sample media (aluminum, vinyl, upholstery) and sample locations within the home (kitchen, bedroom, bathroom, dining room, living room, basement). Also, the treatments are largely meant to be made to inaccessible areas of the house. Dermal exposure is based on a study (Vaccaro, 1991) in which adults (wearing swim suits) crawled on treated carpets for a period of 4 hours. A normalized value of 16,700 cm^2/hour is used for durations of up to 8 hours. OPP is considering other data in which biological monitoring samples following crack and crevice uses were collected. These studies suggest substantially lower internal doses when compared to the Vaccaro data, which were based on immediate contact with carpets following a broadcast application. The differences in internal doses are likely to be associated with the obvious differences in treatment strategies (broadcast vs. along walls and under cabinets) and amounts of carbaryl applied to a given household. In the Vaccaro study, 0.127 grams of ai were applied, in the crack and crevice studies (Byrne, 1998, Krieger, 2001, Hore 2003), 0.002 to 0.42 grams of ai were applied. In addition, the original deposition data collected in the propoxur crack and crevice study was supplemented with additional measurements comparing deposition values and hands rubbed across the same treated surfaces. The current assessment is considered a screen and may be refined if needed.

Duration: The duration of exposure used in the crack and crevice assessment is 8 hours, based on professional judgment. This estimate is based on average number of hours children are awake each day; It does not account for time spent eating, bathing, or time spent outside of the home, when contact with treated surfaces does not occur.

iii. Post-Application Inhalation Exposure

Inhalation post-application exposure was calculated as the product of air concentration (mg/m^3), age-specific breathing rates (m^3/hour), and duration of exposure (hours/day). A further description of each of these terms is presented below:

Air Concentration Data: The chemical specific air concentration data (Knarr, 1988b) used in this assessment combined air samples from the bathroom and kitchen, for the house with the highest monitored air concentrations over the 48 hour sampling period. A lognormal distribution of the hardwood air concentration values

(mean = 0.0053 mg/m^3, standard deviation = 0.0021 mg/m^3) was used in this assessment. Dissipation for inhalation exposure was calculated based on the assumption of 10 % dissipation per day with residue values set to "0" after 1 day.

Breathing Rates: The breathing rates used for this assessment are represented by a uniform distribution from 1 to 2 m^3/hour for light to moderate activity. This assumption is based on information from the EFH (USEPA, 1997). This distribution was used to assess exposure for all age groups.

Duration: The indoor inhalation assessment assumes up to 24 hours of exposure per day. The inhalation duration is based on a cumulative distribution of time spent indoors (EFH Table 5-131).

iv. Post-Application Oral (hand-to-mouth) Exposure

Post-application exposure through the oral (hand-to-mouth) route was also assessed for children ages 1-5. Specifically, exposures through the hand-to-mouth route were calculated as the product of the residue value (mg/cm^2), the frequency of events (hour-1), the surface area of hand mouthed (cm^2), the saliva removal efficiency, the adjustment for wet hands, and the duration of exposure (hours/day).

Ingestion of residues collected by wet hands and subsequently removed by mouthing is estimated in a manner similar to the approach used in the lawn care scenario. The only difference is the use of a 10 percent transferable rate rather than 5 percent, which is captured in the adjustment for wet hands (uniform distribution, minimum value of 1.5, and maximum value of 3). The increased efficiency is based on comparisons of wet vs. dry hands when pressed onto treated carpets and vinyl tiles described by Clothier et al. (1999a, 1999b).

Residue data used in this assessment is the same as that used to assess post-application dermal exposure for the crack and crevice scenario (Knarr, 1988b). All contact factors are the same as those used in the lawn care assessment with one exception. Zartarian (2003) indicated a difference between indoors and outdoors mouthing frequencies. Therefore, the crack and crevice hand-to-mouth scenario is based on indoor frequencies as defined by a Weibull distribution (mean = 13 events/hour, standard deviation = 18 events/hour). The Weibull distribution was truncated at the calculated 80th percentile of the distribution. This was done in order to avoid values that were well beyond those deemed reasonable.

Duration: The duration of exposure used in the crack and crevice hand-to-mouth assessment was 8 hours, based on professional judgement.

g. Pet Collar Scenarios

The preliminary NMC CRA also considered exposures through the use of flea collar products for carbaryl and propoxur. These assessments rely on pet fur transferable residue data for carbaryl. The dermal contact factor(s) for post application exposure is based on a shampoo and groomer exposure study for carbaryl (each groomer shampooed, brushed and groomed 8 dogs). Each groomer shampooed the dogs, picked them up wet to be placed in crates until all the dogs were shampooed. The dogs were then dried and groomed. These activities are likely to result in higher contact factors than intermittent contact with a pet wearing a collar.

i. Applicator Exposure

Applicator exposure was not directly considered in this assessment since it is expected to be minimal when compared to the post application exposure assessment.

ii. Post-Application Dermal Exposure

Post-application dermal exposure scenarios were considered for both adults and children while post-application non-dietary oral exposure scenarios (oral hand-to-mouth) were assumed to apply only to children ages 1-5 years old. This data, as described below, was used to assess the pet collar uses of both carbaryl and propoxur. Frequency, timing, and probability of collar treatments are also incorporated in the preliminary NMC CRA.

Dermal post-application exposure (to adults and children) was calculated as the product of residue concentration (mg/cm^2), the transfer coefficient (in cm^2/hour), and the duration of exposure (hours/day). A further description of each of these terms is presented below:

Residue Concentration: The residue concentration on fur was derived from a study (Emlay et al, 1977) of transferable residues from dogs treated with a flea collar using carbaryl as the active ingredient. This study evaluated the quantity of carbaryl removed (by petting) from dogs of various sizes and hair lengths for a period of up to 7 days after placement of the collars. The average residue measured over the course of this study was 0.0012 mg/cm^2. This value was used as a point estimate. Residues were assumed to be available on a daily basis since pet collar products are designed to

emit residues throughout their active period (120 days for carbaryl and 180 days for propoxur).

Transfer Coefficient: The transfer coefficients used in the dermal post-application exposure assessment was derived from a groomer exposure study (Mester, 1998b) in which sixteen different veterinary personnel treated/handled eight dogs each, over a two to five hour time period. In this assessment, the transfer coefficients for adults and children were derived assuming an average transfer efficiency of 2.97% from the previous OP pet fur residue transfer efficiencies. These efficiencies are similar to the average transfer efficiency calculated from the carbaryl pet collar study data (2.6%). For the preliminary NMC CRA, the data were used directly to generate an empirical distribution for the dermal transfer coefficient. The selected TCs ranged from 180 to 4700 cm^2/hour for adults and from 66 to 1800 cm^2/hour for children. These empirical distributions were used for both pet collar scenarios.

Duration: The time spent in this activity was based on a cumulative distribution, ranging from 0 to 2.3 hours/day for children and 0 to 4.7 hours/day for adults. This distribution was taken from the EFH (USEPA, 1997), Table 15-77 for time spent in animal care. In this assessment, the duration of exposure is assumed to be continuous contact rather than the intermittent contact normally associated with pet care (e.g. walking, feeding). Furthermore, dog collar residues are likely to be localized around the neck, and therefore, contact with other areas of the pet will result in little to no exposure. OPP is attempting to draw the distinction between direct contact with a treated pet and the time spent with a pet where there is limited contact. For example, time spent with pets in and around the house or sleeping in the same bed may not result in direct contact for the entire duration. The pet collar scenario assessed in the preliminary NMC CRA uses pet fur residues transferred to individuals at a rate found during a study of shampooing and grooming, for a duration of up to 4.7 hours. Use of this data to represent residential exposure to pets is likely to encompass all other potential exposure scenarios involving direct or indirect contact with treated pets.

iii. Oral (Hand-to-Mouth) Post-Application Exposure

Post-application exposure through the oral (hand-to-mouth) route was also assessed for children ages 1-5. Specifically, exposures through the hand-to-mouth route were calculated as the product of the residue concentration (mg/cm^2), the frequency of events (hour-1), the surface area of hand mouthed (cm^2), saliva removal efficiency, adjustment for wet hands, and the duration of exposure (hours/day).

The residue data (Emlay et al, 1977) and duration of exposure values (USEPA, 1997/Table 15-77) used for the non-dietary exposure assessment are the same as those used in the dermal post-application assessment for the pet collar scenarios presented above. All contact factors (frequency of hand to mouth events (Zartarian, 2003), surface area of hand mouthed (Zartarian, 2003), saliva extraction factor (Geno et al., 1995; Fenske and Lu 1994; Wester and Maibach 1989)) are the same as those used in the crack and crevice assessment. As discussed in that scenario, non-dietary ingestion may be overestimated based on the assumed replenishment the hand with residues from the pet for each mouthing event. Also, because the frequency (number of events) and surface area of the hand mouthed per event are fixed for each individual iteration, an upper percentile value for each variable may overestimate exposure. For example, 99 events per hour times 20 cm^2 per hour is equal to 1980 cm^2. These values, coupled with a long duration (four hours), the large surface area mouthed (7920 cm^2, are likely to exceed the surface area of most pets.

h. Golf Course Scenario

i. Post-Application Dermal Exposure

Carbaryl is also used on golf courses. The current assessment addresses dermal post-application exposure for adults and teens playing rounds of golf on treated courses. Post application exposure was estimated as the product of turf-transferable residue (mg/cm^2), transfer coefficient (cm^2/hour), and time spent in the activity (hours).

The percent of the population playing golf and the percent of golf courses that are treated with carbaryl was also considered and incorporated into the assessment. The *1992 Golf Course Operations: Cost of Doing Business/Profitability* survey conducted by the Center for Golf Course Management (CGCM) was used to establish the percent of individuals playing golf. The CGCM survey reported that an average of 12% of the population plays golf. To determine the likelihood of playing golf on a treated golf course, percent of golf courses treated data provided by Doane's GolfTrak (1998-1999) was used. These data indicated up to 25% of golf courses are treated with carbaryl, depending upon the region of use.

Residue Data: Since liquid broadcast applications to golf course turf are permitted, the liquid TTR data (Mester, 1999) used to assess post-application exposure for the lawn care scenario was also used to assess risk for this scenario.

Transfer Coefficients: The surrogate data used to derive transfer coefficients were based on two measurements of four individuals playing golf on two golf courses treated with chlorothalonil (Ballee, 1990), and the exposure of golfers (four volunteers) to flurprimidol (Moran et al, 1987). For both studies, an assumed transfer efficiency of 1% was used to calculate the transfer coefficients, since the studies were conducted using spray-able formulations. Based on these two studies, a lognormal distribution with a mean of 480 cm^2/hour and a standard deviation of 160 cm^2/hour was used to represent the transfer coefficient. This distribution was truncated at the calculated 99th percentile value of 960 cm^2/hour. All transfer coefficients are based on individuals wearing short sleeved shirts and short pants. A reduction factor was applied to account for body weight and surface area differences for adults and teenagers.

Duration: The exposure duration for individuals playing golf was assumed to be a uniform distribution bounded at the low end by two hours and at the upper end at four hours. The four-hour value was obtained from the CGCM survey.

F. The Multi-Pathway Cumulative Assessment

The previous sections of this document have described the development of the major components of the risk assessment. They describe a highly complex process of combining multiple data sets to develop a description of the possible risks from NMC pesticides by each of the pathways described. OPP has had to develop new methods for each component of the assessment in order to produce an assessment, which presents as realistically as possible the potential exposure to NMC pesticides. The purpose of this section is to explain the concepts used to accumulate risk from each pathway into a total risk estimate, summarize some of the major preliminary findings, and to provide a basis for understanding the graphical temporal exposure profiles that are provided in the Appendices.

1. Basic Concepts

The definition of cumulative risk developed as a result of the passage of FQPA requires OPP to conduct a risk assessment for a group of pesticides with a common mechanism of toxicity that is multi-pathway, multi-route, and multi-chemical in scope. As described in section I.B of this preliminary cumulative assessment for the NMCs, the RPF method was used to address the issue of combining toxic responses from NMCs with varying propensities to inhibit acetyl cholinesterase. Exposure to each NMC was normalized to equivalent exposure to the index compound, oxamyl. The toxicity data currently available for conducting this analysis are estimates of response by route-specific dosing, and do not support estimating delivered dose to the target tissue. OPP decided to address this problem by comparing route-specific exposures to route-specific points of departure to produce unitless margins of exposure for each route. In this case, the POD was a BMD_{10}. MOEs were combined by taking the inverse for each route, adding them together, and then taking the inverse of that sum. This process was used to produce a distribution of daily estimates for the subpopulation of concern that reflects regional and seasonal variation[6] in the patterns of exposure that are likely to occur throughout the US across the year. OPP used a probabilistic assessment to capture the full range of exposure possibilities from all sources analyzed. The intent was to produce an estimate of risk that is as realistic as possible. The NMC cumulative risk assessment is not a high end risk assessment for the specific situation, e.g., geographic location. Without underestimating exposure by a significant pathway, we believe it reflects the full range of likely exposures for consideration in a regulatory context and tries to avoid developing extreme exposure estimates based upon the combination of exposure scenarios and assumptions that are not reasonable.

[6] Note that seasonal variation was only considered for the residential and drinking water pathways. No seasonal variation was considered for the food pathway.

2. Framing the Population-Based Assessment

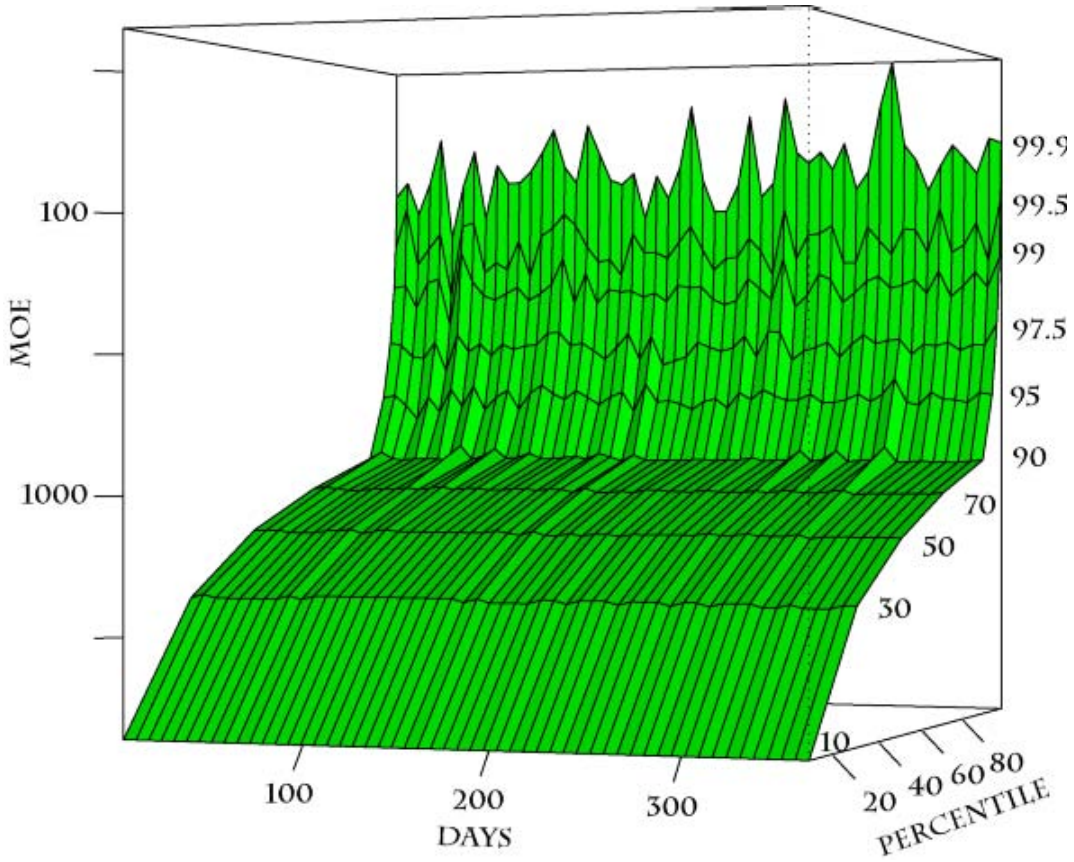
OPP used the above-described methodologies to develop a series of daily exposure distributions and array them as a distribution across time. The distribution of daily exposures and resulting MOEs are developed such that the exposures from NMCs in foods, drinking water and from residential uses are all calculated simultaneously for each hypothetical individual in the subpopulation. OPP used the Calendex software to develop the distributions and resulting MOEs. Calendex permits incorporation of time course information with regard to residential uses of pesticides and exposures through water, but does not permit specific allowance for regional variability. As described in section I.D OPP addressed this issue by focusing its preliminary risk assessment on regional locations that represent what is likely to be the most vulnerable drinking water sources in high carbamate use areas. Based on a comparison of estimated drinking water exposures from surface- and ground-water sources in eight regions, OPP selected drinking water exposures representing the two most vulnerable areas – the Coastal ridge of Florida (private wells) and the southeastern coastal plain of North Carolina (private wells and public surface water) – for the multi-pathway assessment. NMC exposures in drinking water from the remaining parts of the country are expected to be substantially lower than from these sites.

To generate a daily distribution of exposure for the subpopulation of interest, a consumption record is selected from the CSFII that corresponds to the age group of interest. Calendex uses this consumption record to estimate NMC exposure from food by randomly assigning a residue value for each food included. After multiplying each amount of food consumed by its selected residue value, the total exposure for this individual from food is summed. At the same time, all appropriate residential scenarios that may be encountered for the calendar day 1 (January 1) are reviewed. A probability-based decision is made as to whether or not that scenario will be encountered (e.g., a lawn treatment; probably not in January). If the scenario is assigned a "yes" answer, then the appropriate values defining the exposure are selected from the many distributions of input parameters for residential exposure scenarios. Dermal, oral and inhalation exposures are calculated for all selected residential scenarios. A drinking water value taken from the estimated distribution of water residues for January 1 is selected and paired with the water consumption reported in the CSFII consumption record. These values are used to calculated exposure from drinking water for that date. All of the exposures are converted to route-specific MOEs to define the total exposure to the hypothetical individual on January 1. The process is repeated for each consumption record for the age group in the CSFII one hundred times to build a distribution of exposures for January 1. This process is repeated for January 2, January 3 and so forth across the same year.

The 365 daily exposure distributions are arrayed together in order to provide a profile of possible exposures by each route and in total as MOEs. A hypothetical example of such a distribution of distributions is presented in Figure I.F.1. In this figure, each daily distribution is arrayed on the yz plane of the plot.

Day 365 can be clearly seen on the right side of the plot. This distribution of total risk is expressed as a cumulative distribution function of MOEs versus percentile of exposure. Percentile of exposure refers to that portion of the population that has less than or equal exposure. For example, 80 % of the population has an exposure level that is equal to or less than the 80th percentile.

Figure I.F.1. Three-dimensional plot of the total MOE by day of the year and percentile of exposure



3. Interpreting the Outputs

The results of the final assessment are presented in graphical form in the appendices. They reflect year-long slices across the 3-dimensional plot in Figure I.F.1. In that plot, dark lines can be seen across the total MOE surface. For instance, the top line in the 3-dimensional plot represents the 99.9th percentile of exposure for the population. A slice through the surface parallel to the xy plane at the 99th percentile would look like the plot presented in Figure I.F.2. This plot presents the potential total MOE for the population exposed to NMCs by the exposure scenarios included in this assessment. In addition, the contributions from various pathways and routes of exposure are arrayed separately to assist the risk manager in identifying contributors to risk for further evaluation. Other percentiles of exposure may also be of interest.

OPP will use the changes in graphical presentations of data such as these to evaluate the significance of various sources of exposure, considering the percentile at which the exposure becomes significant and the duration over which the exposure route and source remain dominant in the risk assessment results.

4. Attributes of the Preliminary N-Methyl Carbamate Cumulative Risk Assessment

The current preliminary assessment focuses on estimating the potential risk from exposure to 10 N-methyl carbamate pesticides in food and drinking water and from residential uses. The assessment is limited in geographic scope to the Southern area of the U.S. This limitation was placed on the assessment to ensure that the water and residential components of the assessment would reflect what a coherent set of pesticide uses are likely to exist. Understanding the likelihood of co-occurrence of pesticide uses is critical to developing a reasonable estimate of total cumulative risk. In the absence of direct measures of co-occurrence, overlapping exposures must be extrapolated from use data.

As indicated previously in this report, Table I.B.7 for the food and residential components of the cumulative risk assessment, a PoD was used for the oral component of the total cumulative risk assessment. The estimated $BMDL_{10}$ (0.14 mg/kg body wt/day) for brain AChE inhibition by the index compound (oxamyl) was used. The inhalation and dermal components of the assessment were compared to $BMDL_{10}$'s of 0.05 and 17.05 mg/kg body wt/day, respectively.

Integrated cumulated risk assessments were conducted for the age groups of, Children 1-2 years, Children 3-5 years, Adults 20-49 years, and Adults 50+ years of age. These four groups were chosen to emphasize the effects of differences in behavior and food consumption patterns on estimating the risk from exposure to pesticides. The assessments reflect the same assumptions about use scenarios, timing of exposures and exposures to pesticides in food and water as used in the previous pathway specific assessments. An entire year of exposure is simulated. Three different water scenarios from the south were matched with a residential scenario that used southern application timing patterns. Two water scenarios simulated ground water sources in Florida and North Carolina and one scenario represented a surface water source in North Carolina.

The food component of the cumulative risk assessment contains as many commodities as could reasonably be extrapolated from the available PDP and FDA monitoring data. This component of the assessment is regarded as highly refined and reflective of exposures likely to be encountered by the U.S. population. Because data on residential exposure are more limited, the residential component of the assessment was also designed to reflect some overestimation bias to ensure that risk from these sources of exposure were not likely to be underestimated. As has been noted in previous chapters, additional

refinements are planned.[7] The water components of the assessment focused on what OPP believes are the most vulnerable drinking water sources. While the estimated drinking water concentrations are reasonable reflections of actual exposures in those particular areas, the rest of the country is expected to have substantially lower NMC residue levels in its drinking water.

As discussed earlier, exposures estimates are specific to the regions discussed; they take into account region-specific water and residential use practices and cannot – as a general matter – be necessarily extrapolated to different regions. The Florida groundwater scenario is specific to an area in Florida in which the use of NMC pesticides, particularly aldicarb, is high, soils are highly permeable, the depth to groundwater is shallow, and the soils and water are acidic. These conditions are favorable to potentially high levels of NMC residues in drinking water sources. The North Carolina coastal plain groundwater scenario represents another area where high NMC use, dominantly aldicarb, highly permeable soils, shallow ground water and acidic conditions are likely to favor potentially high NMC levels. Further description of these sites and the conditions and characteristics that led OPP to select these sites as high-end with respect to ground water concentrations is described in Section D of this document. OPP notes that NMC drinking water concentrations in the much of the rest of the U.S. would be expected to be substantially lower such that exposure through drinking water would be a negligible.

Estimates of cumulative risk from 10 N-methyl carbamates associated with exposure through foods, drinking water, and residential uses are presented in Appendices II.F.1-3 for Children 1-2 years old, Children 3-5 years old, Adults 20-49 years old and for Adults 50+. The contributions of each of the major routes of exposure and the likely sources of those exposures are discussed in previous sections of this preliminary assessment. Graphical presentations are limited to the 95th, 99th, and 99.9th percentiles because these percentiles capture the higher end of exposure which has traditionally been of most interest to the Agency.

a. Children, 1-2 years, Florida Coastal Ridge Ground Water

The results of the total cumulative assessment for Children 1-2 years using the $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.F.1 Temporal Exposure Profile Plot for Florida Central Ridge Ground Water in Figures II.F. 1-1, II.F.1-2, and II.F.1-3.

<u>95th Percentile</u> - The significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through the drinking water pathway with total MOE's ranging from 25 to approximately 300 (Figure II.F.1-1). The food component of the assessment was stable across time with an MOE that is generally near 1000 across the year. Inhalation and dermal exposures that are associated with residential use rarely occur at

[7] For example, TTR values for the liquid formulation of carbaryl were the only ones available and broadcast use of only the granular formulation is now permitted. Nevertheless, this assessment used the TTR's associated with the liquid formulation.

this percentile because typically only a small percentage of the population uses such products.

99th Percentile – The daily total MOEs ranged from 15 to 100. At this percentile, the daily MOE values from drinking water sources ranged from 15 to ca. 200 and comprise the major source for total exposure. MOEs from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were somewhat lower than drinking water exposure and generally the MOEs for oral non-dietary exposure pathway ranged from ca. 180 to greater than 10,000 (Figure II.F.1-2). MOE's associated with food pathways were generally around 200. MOE's associated with the dermal route are generally greater than 1000 but as low as ca. 540. Inhalation exposure is not yet seen for children 1-2.

99.9th Percentile – At the 99.9th percentile, the total cumulative risk (all pathways) was as low as 10 for this age group and nearly all of the estimated exposure came through the oral route that included significant contributions from oral non-dietary, drinking water and food pathways (Figure II.F.1-3). Oral non-dietary exposure (hand-to-mouth) resulted in MOEs remaining consistent through the year between ca 20 and 170. Dermal MOEs go down to ~ 50 from day 100 to day 140 and are greater than 100 during the first 100 days of the year and remained near 1,000 after day 300. Inhalation MOEs were greater than ca. 2,500 when they occurred.

b. Children 3-5 years, Florida Coastal Ridge Ground Water

The results of the total cumulative assessment for Children, 3-5 years old using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.F.1 Temporal Exposure Profile Plot for Florida Central Ridge Ground Water in Figures II.F.1-4, II.F.1-5, and II.F.1-6.

95th Percentile – Total MOEs at this percentile range from 30 to 250 throughout the year. The significant contributor to total cumulative exposure comes through the drinking water pathway (Figure II.F.1-4) with a range of MOEs of ca. 30 to ca. 300. The next most significant contributor to total cumulative exposure is through the food pathway; this pathway has fairly stable MOEs of slightly greater than 1000. As with Children 1-2 years old, Inhalation and dermal exposures do not occur at this percentile.

99th Percentile - At this percentile, the MOE from drinking water sources generally remained in the 20 to 100 range and are essentially equivalent to total (cumulative) exposure since the drinking water pathway predominated. MOE's associated with food were generally near 200. Exposures from oral non-dietary ingestion (i.e., hand-to-mouth) was less than exposure from drinking water and food and MOEs for this source

generally ranged from ca. 300 to greater than 10,000 (Figure II.F.1-5). MOE's associated with the dermal route appear for the first time here and always exceed ca. 700. As with Children 1-2 years old, inhalation exposures do not occur at this percentile.

99.9th Percentile – At the 99.9th percentile, the total MOE (all pathways) was in the 10-30 range for this age group and this was nearly all contributed by food, drinking water, oral non-dietary, and dermal exposure (Figure II.F.1-6). Oral non-dietary exposure (hand-to-mouth) is next in importance with MOEs as low as 30. MOE's varied for exposure through food around 40. MOEs for dermal exposures generally ranged between 60 and 1000 during the first 120 days of the year. MOEs associated with inhalation exposure occurred infrequently and when they did occur were above 2400 throughout the year.

c. Adults, 20-49 years, Florida Coastal Ridge Ground Water

The results of the total cumulative assessment for Adults, 20-49 years using the $BMDL_{10}$ for the PoD are presented in Appendix II.F.1 Temporal Exposure Profile Plot for Florida Central Ridge Ground Water in Figures II.F.1-7, II.F.1-8, and II.F.1-9.

95th Percentile - Total MOEs at this percentile are in the 80 to 300 range with contributions from drinking water dominant and persistent throughout the year; exposures through the food pathway contribute a relatively small amount compared to total exposure, with MOEs for food above 1400 (Figure II.F.1-7). Dermal MOEs were all greater than 100,000. Inhalation exposure, which is associated with residential use rarely, occurs at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – Total MOE's are generally in the 30 to 250 range at this percentile, with exposure from drinking water dominating during the entire year (Figure II.F.1-8). MOE's associated with food are generally in the neighborhood of 600. Dermal exposures are associated with MOEs of approximately 1300 to greater than 10,000. Exposures through the inhalation route are not yet seen at this percentile.

99.9th Percentile –Total MOE's at this percentile are generally in the 20-100 range, with exposure from drinking water dominant almost throughout the year (Figure II.F.1-9). MOE's associated with food are generally in the neighborhood of 100. Dermal exposures are associated with MOEs of approximately 100 to greater than 2,000. Exposures through the inhalation route are not yet seen at this percentile.

d. Adults, 50+ years, Florida Coastal Ridge Ground Water

The results of the total cumulative assessment for Adults, 50+ years using the $BMDL_{10}$ for the PoD are presented in Appendix II.F.1 Temporal Exposure Profile Plot for Florida Central Ridge Ground Water in Figures II.F.1-10, II.F.1-11, and II.F.1-12.

95th Percentile - Total MOEs at this percentile are in the 80 to 300 range with contributions from drinking water all year long and food contributing a relatively small amount of exposure resulting in MOEs above 1400 and dermal MOEs were all greater than 10,000 (Figure II.F.1-10). Inhalation exposure, which is associated with residential use rarely, occurs at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – Total MOE's are generally in the 30 to 230 range at this percentile, with exposure from drinking water dominating during the entire year (Figure II.F.1-11). MOE's associated with food are generally in the neighborhood of 500. Dermal exposures are associated with MOEs of approximately 1400 to greater than 5,000. Exposures through the inhalation route are not yet seen at this percentile.

99.9th Percentile –Total MOE's at this percentile are generally in the 20 to 100 range, with exposure from drinking water dominant almost throughout the year (Figure II.F.1-12). MOEs from exposure through the food pathway were in ca. 100. Dermal exposures are associated with MOEs of generally ca. 175 to 2000 while those associated with the inhalation route are generally near the 6,800 to greater than 10,000 ranges.

e. Children, 1-2 years, North Carolina Coastal Plain Ground Water

The results of the total cumulative assessment for Children, 1-2 years using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.F.2 Temporal Exposure Profile Plot for North Carolina Coastal Plain Ground Water in Figures II.F.2-1, II.F.2-2, and II.F.2-3.

95th Percentile - The significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through the drinking water pathway with total MOE's ranging from 74 to 80 (Figure II.F.2-1). The food component of the assessment was stable across time with an MOE that is generally near 1000 across the year. Inhalation and dermal exposures, which are associated with residential use, occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile - At this percentile, the daily MOE values from drinking water sources were ca. 50 and comprise the major source for total

exposure. Exposures from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were somewhat lower than drinking water exposure and generally the MOEs for oral non-dietary exposure pathway ranged from ca. 190 to greater than 10,000 (Figure II.F.2-2). MOE's associated with food were generally around 200. MOE's associated with the dermal pathway are generally greater than 1000 but as low as ca. 540. Inhalation exposure is not yet seen for children 1-2.

99.9th Percentile – At the 99.9th percentile, the total cumulative risk (all pathways) generally was in the 13-28 range for this age group and was nearly all of the estimated exposure came through the dermal, drinking water and food pathways (Figure II.F.2-3). Oral non-dietary exposure (hand-to-mouth) resulted in MOEs remaining consistent through the year between 22 and 170. Dermal MOEs generally ranged between ca. 50 and greater than 100 during the first 300 days of the year and greater than 1,000 during the remainder of the year. Inhalation MOEs were greater than ca. 2,500 when they occurred.

f. Children 3-5 years, North Carolina Coastal Plain Ground Water

The results of the total cumulative assessment for Children, 3-5 years old using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.F.2 Temporal Exposure Profile Plot for North Carolina Coastal Plain Ground Water in Figures II.F.2-4, II.F.2-5, and II.F.2-6.

95th Percentile – Total MOEs at this percentile are approximately 85 throughout the year. The significant contributor to total cumulative exposure comes through the drinking water pathway (Figure II.F.2-4) with an MOE of ca. 90. The next most significant contributor to total cumulative exposure is through the food pathway; this pathway has fairly stable MOEs of slightly greater than 1000. Inhalation and dermal exposures which are associated with residential uses rarely occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile - At this percentile, the MOE from drinking water sources generally remained in the 60 range and are essentially equivalent to total (cumulative) exposure since the drinking water pathway predominated. MOE's associated with food were generally near 200. Exposures from oral non-dietary ingestion (i.e., hand-to-mouth) was less than exposure from drinking water and food and MOEs for this source generally ranged from ca. 260 to greater than 10,000 (Figure II.F.2-5). MOE's associated with the dermal route appear for the first time here and always exceed ca. 700. As with Children 1-2 years old, inhalation exposure is not seen at this percentile.

99.9th Percentile – At the 99.9th percentile, the total MOE (all pathways) was in the 17 to 27 range for this age group and this was nearly all contributed by drinking water (Figure II.F.2-6). Oral non-dietary exposure (hand-to-mouth) is next in importance with MOEs as low as 30. MOE's varied for exposure through food around 40. MOEs for dermal exposures generally ranged between 60 and 1000 during the first 120 days of the year. MOEs associated with inhalation exposure occurred infrequently such that they are not seen in the figure and when they did occur were above 2400 throughout the year.

g. Adults, 20-49 years, North Carolina Coastal Plain Ground Water

The results of the total cumulative assessment for Adults, 20-49 years using the $BMDL_{10}$ for the PoD are presented in Appendix II.F.2 Temporal Exposure Profile Plot for North Carolina Coastal Plain Ground Water in Figures II.F.2-7, II.F.2-8, and II.F.2-9.

95th Percentile - Total MOEs at this percentile are in the 130 to 140 range with contributions from drinking water dominant and persistent throughout the year; exposures through the food pathway contribute a relatively small amount compared to total exposure, with MOEs for food above 1400 (Figures II.F.2-7). Dermal MOEs were all greater than 100,000. Inhalation exposure, which is associated with residential use rarely, occurs at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – Total MOE's are generally in the 70 to 90 range at this percentile, with exposure from drinking water dominating during the entire year. Drinking water MOE's were constantly about 85. MOE's associated with food are generally in the neighborhood of 600 (Figure II.F.2-8). Dermal exposures are associated with MOEs of approximately 1300 to greater than 10,000. Exposures through the inhalation route are not yet seen at this percentile.

99.9th Percentile –Total MOE's at this percentile are generally in the 35 to 55 range, with exposure from food and drinking water dominant almost throughout the year with individual pathways resulting from MOEs of in the neighborhood of 100 for food and 40 for drinking water pathways (Figure II.F.2-9). Dermal exposures are associated with MOEs of generally ca. 100 to greater than 2000 while those associated with the inhalation route are generally near the 600 to greater than 10,000 range.

h. Adults, 50+ years, North Carolina Coastal Plain Ground Water

The results of the total cumulative assessment for Adults, 50+ years using the $BMDL_{10}$ for the PoD are presented in Appendix II.F.2

Temporal Exposure Profile Plot for North Carolina Coastal Plain Ground Water in Figures II.F.2-10, II.F.2-11, and II.F.2-12.

95th Percentile -.Total MOEs at this percentile are ca. 140 with contributions from drinking water all year long and food contributing a relatively small amount of exposure resulting in MOEs above 1400 and dermal MOEs were all greater than 10,000 (Figure II.F.2-10). Inhalation exposure which is associated with residential use rarely occurs at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – Total MOE's were generally around 100 at this percentile, with exposure from drinking water dominating during the entire year. MOE's associated with food are generally in the neighborhood of 500 (Figure II.F.2-11). Dermal exposures are associated with MOEs of approximately 1400 to greater than 5,000. Exposures through the inhalation route are not yet seen at this percentile.

99.9th Percentile –Total MOE's at this percentile are generally in the 50 to 60 range, with exposure from drinking water dominant almost throughout the year (Figure II.F.2-12). MOEs from exposure through the food pathway were in ca. 100. Dermal exposures are associated with MOEs of generally ca. 175 to 2000 while those associated with the inhalation route are generally near the 6,800 to greater than 10,000 ranges.

i. Children, 1-2 years, North Carolina Coastal Plain Surface Water

The results of the total cumulative assessment for Children, 1-2 years using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.F.3 Temporal Exposure Profile Plot for North Carolina Coastal Plain Surface Water in Figures II.F.3-1, II.F.3-2, and II.F.3-3.

95th Percentile - The significant source of pesticide risk from exposure to pesticides at this percentile of exposure is through the food pathway with total MOE's ranging from 470 to approximately 970 (Figure II.F.3-1). The food component of the assessment was stable across time with an MOE that is generally near 1000 across the year. Drinking water exposure resulted in MOEs as low as 1400 for a short period of time, from day 106 to day 167. Inhalation and dermal exposures, which are associated with residential use rarely, occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile - MOE's associated with food were generally around 200 and comprise the major source for total exposure. Exposures from oral non-dietary ingestion which are associated with residential use (i.e., hand-to-mouth) were somewhat lower than drinking water exposure and

generally the MOEs for oral non-dietary exposure pathway ranged from ca. 130 to greater than 10,000 (Figure II.F.3-2). At this percentile, the daily MOE values from drinking water sources ranged from 750 to greater than 10,000. MOE's associated with the dermal pathway are generally greater than 1000 but as low as ca. 540. Inhalation exposure is not yet seen for children 1-2.

99.9th Percentile – At the 99.9th percentile, the total cumulative risk (all pathways) generally was in the 15-30 range for this age group and was nearly all of the estimated exposure came through the oral route comprised mostly of drinking water and food pathways (Figure II.F.3-3). Oral non-dietary exposure (hand-to-mouth) is next in importance with MOEs varied through the year from about 25 to 170. Dermal MOEs generally ranged between 50 and greater than 100 during the first 300 days of the year and remained near 5,000 during the remainder of the year. Inhalation MOEs were greater than ca. 2000 when they occurred.

j. Children 3-5 years, North Carolina Coastal Plain Surface Water

The results of the total cumulative assessment for Children, 3-5 years old using the estimated $BMDL_{10}$ of the index chemical (oxamyl) for the PoD are presented in Appendix II.F.3 Temporal Exposure Profile Plot for North Carolina Coastal Plain Surface Water in Figures II.F.3-4, II.F.3-5, and II.F.3-6.

95th Percentile – Total MOEs at this percentile are approximately 500 to 1000 throughout the year. The significant contributor to total cumulative exposure comes through the food pathway (Figure II.F.3-4) with a range of MOEs of ca. 1000 to 1100. The next most significant contributor to total cumulative exposure is through the drinking water pathway; this pathway has MOEs of greater than 1400. Inhalation and dermal exposures, which are associated with residential use rarely, occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile - The total (cumulative) exposure was in the 90 to 190 range with most of the exposure delivered through exposure to food. At this percentile, the MOE from food sources generally remained between 180 and 210. The drinking water pathway ranged in MOEs from 800 to greater than 10,000. MOEs for oral non-dietary ingestion (i.e., hand-to-mouth) generally ranged from ca. 260 to greater than 10,000 (Figure II.F.3-5). MOE's associated with the dermal route appear for the first time here and always exceed ca. 700. As with Children 1-2 years old, inhalation and dermal exposures do not occur at this percentile.

99.9th Percentile – At the 99.9th percentile, the total MOE (all pathways) was in the 20 to 40 range for this age group and this was nearly all contributed by exposure through the oral route (drinking water, oral non-dietary and food pathways all contributed to these MOEs) (Figure II.F.3-6).

Oral non-dietary exposure (hand-to-mouth) is important with MOEs generally in the 30 to 1000 range throughout the year. MOE's varied for exposure through food around 40. MOEs for dermal exposures generally were above 100 although there were some days where the dermal MOE was as low as ca. 60. MOEs associated with inhalation exposure occurred infrequently and when they did occur were above 1000 throughout the year.

k. Adults, 20-49 years, North Carolina Coastal Plain Surface Water

The results of the total cumulative assessment for Adults, 20-49 years using the $BMDL_{10}$ for the PoD are presented in Appendix II.F.3 Temporal Exposure Profile Plot for North Carolina Coastal Plain Surface Water in Figures II.F.3-7, II.F.3-8, and II.F.3-9.

95th Percentile -.Total MOEs at this percentile are around 1400 with contributions from food dominant and persistent throughout the year; exposures through the drinking water pathway contribute a relatively small amount compared to total exposure, with MOEs for drinking water above 1400 (Figure II.F.3-7). Dermal MOEs were all greater than 10,000. Inhalation exposure, which is associated with residential use rarely, occurs at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – Total MOE's are generally in the 370 to 660 range at this percentile, with exposure from food dominating during the entire year (Figure II.F.3-8). MOE's associated with food are generally in the neighborhood of 600. Drinking water MOEs ranged from ca. 1200 to greater than 10,000. Dermal exposures are associated with MOEs of approximately 1300 to greater than 10,000. Exposures through the inhalation route are not yet seen at this percentile.

99.9th Percentile –Total MOE's at this percentile are generally in the 50-110 range, with exposure from food dominant almost throughout the year (Figure II.F.3-9). Dermal exposures are associated with MOEs of generally ca. 100 to 2000 while those associated with the inhalation route are generally near the 1,600 to greater than 10,000 range.

l. Adults, 50+ years, North Carolina Coastal Plain Surface Water

The results of the total cumulative assessment for Adults, 50+ years using the $BMDL_{10}$ for the PoD are presented in Appendix II.F.3 Temporal Exposure Profile Plot for North Carolina Coastal Plain Surface Water in Figures II.F.3-10, II.F.3-11, and II.F.3-12.

95th Percentile -.Total MOEs at this percentile are in the 1300 to 3000 range with contributions from food all year long. Drinking water

contributed a relatively small amount of exposure resulting in MOEs above 1400 and dermal MOEs were all greater than 10,000 (Figure II.F.3-10). Inhalation and dermal exposures which are associated with residential use rarely occur at this percentile because typically only a small percentage of the population uses such products.

99th Percentile – Total MOE's are generally in the 400 to 560 range at this percentile, with exposure from food dominating during the entire year. MOE's associated with drinking water range from 1250 to greater than 10,000 (Figure II.F.3-11). Dermal exposures are associated with MOEs of approximately 1200 to greater than 5,000. Exposures through the inhalation route are not yet seen at this percentile.

99.9th Percentile –Total MOE's at this percentile are generally in the 100 range, with exposure from food dominant throughout the year (Figure II.F.3-12). MOE's associated with drinking water range from 670 to greater than 10,000. Dermal exposures are associated with MOEs of generally ca. 180 to 2000 while those associated with the inhalation route are generally near the 5,000 to greater than 10,000 ranges and not frequent enough to show on the graph.

G. Comparison of DEEM/Calendex, Lifeline, and CARES Results

Sections C, D, and E of this preliminary NMC CRA focused on the output and results from the DEEM/Calendex program, emphasizing the food, drinking water, and residential pathways, respectively. Section F of the document provided an integrated discussion of the results, and again focused on the output of the DEEM/Calendex model.

OPP also performed similar analyses with the Lifeline and CARES models.[8] This section of the preliminary NMC CRA reviews and compares the results from all three models.

1. Comparison of DEEM/Calendex, Lifeline, and CARES Exposure and Risk Estimates through the Food Pathway

Estimated Exposures

Table I.G.1 presents the exposure (mg/kg/day) and risk (MOE) estimates for the three models for the subpopulations considered in this preliminary NMC CRA. All models have comparable results at the 95th, 99th, and 99.9th percentiles.

Table I.G.1 Estimated Exposures and Risk from Food Only

	95th Percentile		99th Percentile		99.9th Percentile	
Model	**Exp***	**MOE**	**Exp***	**MOE**	**Exp***	**MOE**
Infants < 1 years old						
DEEM/Calendex	0.000041	3415	0.000189	741	0.001288	109
CARES	0.000036	3892	0.000170	823	0.001257	111
Lifeline	0.000045	3128	0.000180	779	0.001189	118
1 to 2 yr olds						
DEEM/Calendex	0.000143	979	0.000745	188	0.003773	37
CARES	0.000133	1053	0.000720	194	0.003771	37
Lifeline	0.000130	1076	0.000666	210	0.004207	33
3 to 5 yr olds						
DEEM/Calendex	0.000128	1094	0.000696	201	0.003368	42
CARES	0.000117	1199	0.000688	204	0.003449	41
Lifeline	0.000122	1151	0.000672	208	0.003474	40
20 to 49 yr olds						
DEEM/Calendex	0.000034	4118	0.000221	633	0.001279	109
CARES	0.000036	3913	0.000231	605	0.001278	110
Lifeline	0.000037	3812	0.000223	628	0.001389	101

* Exposures are in mg/kg/day in oxamyl equivalents

[8] All three models have cumulated food and water exposures. For DEEM/Calendex, all residential scenarios were assessed and cumulated with food and water for a final cumulative risk assessment. For CARES, residential exposure/risk from post application scenarios for children 1-2 and 3 to 5 for lawn care, pet care, and home crack and crevice are working and the Agency is analyzing the results. For LifeLine, no residential runs were completed.

It is important to note that these models will not (and are not expected to) produce identical results since the various food diaries are used with different expected frequencies, the models apply slightly different weights to project simulated person-days to characterize the exposure of the entire population, and (for LifeLine) modeled bodyweights are used rather than the CSFII reported bodyweights to calculate food consumption (grams/kg bwt)[9] Since these modeling differences vary by age group and are specific to the food residues, we would not expect one model to consistently produce higher or lower estimates than another model, across all age groups, at any given percentile, or across all percentiles for any particular age group.

While model estimates vary slightly from run to run, for the most part, given a reasonable number of iterations, food only, water only, and food plus water results agree between models within a few percent. This is not surprising since the models use similar input data and similar calculations to estimate both risk and exposure. A similar agreement between the model's food, water, and food plus water exposure estimates was seen in the OP Cumulative Risk Assessment.

[9]These models were discussed during the April 29-30 SAP entitled "A Model Comparison: Dietary and Aggregate Exposure in Calendex, CARES, and Lifeline" (USEPA, 2004b). Information and background on this SAP is available at the SAP website (www.epa.gov/scipoly/sap). These SAS model approximations produced similar predictions as the corresponding models for this preliminary NMC CRA.

2. Comparison of DEEM/Calendex, Lifeline, and CARES Exposure and Risk Estimates through the Water Pathway

Table I.G.2. presents the exposure (mg/kd/day) and risk (MOE) estimates from each of the three models for Florida groundwater water residues for the children and adult subpopulations. As was seen in the Section F where the results for the DEEM/Calendex analyses were presented and described, exposures through water at the upper percentiles are substantially higher than from food for all models.

Table I.G.2. Estimated Exposures and Risk from Water Only (FL Groundwater)

	95th Percentile		99th Percentile		99.9th Percentile	
Model	**Exp***	**MOE**	**Exp***	**MOE**	**Exp***	**MOE**
Infants < 1 years old						
DEEM/Calendex	0.008145	17	0.013532	10	0.021160	7
CARES	0.007861	18	0.013180	11	0.020710	7
Lifeline	0.006549	21	0.009427	15	0.012552	11
1 to 2 yr olds						
DEEM/Calendex	0.003546	39	0.006246	22	0.011158	13
CARES	0.003650	38	0.006483	22	0.012000	12
Lifeline	0.003676	38	0.006503	22	0.009841	14
3 to 5 yr olds						
DEEM/Calendex	0.003105	45	0.005427	26	0.009502	15
CARES	0.003050	46	0.005274	27	0.009033	15
Lifeline	0.003026	46	0.005511	25	0.008011	17
20 to 49 yr olds						
DEEM/Calendex	0.002013	70	0.003587	39	0.007251	19
CARES	0.002069	68	0.003308	42	0.006697	21
Lifeline	0.001528	92	0.002958	47	0.005359	26

* Exposures are in mg/kg/day in oxamyl equivalents

3. Comparison of DEEM/Calendex, Lifeline, and CARES Exposure and Risk Estimates through the Food + Water Pathway

Table I.G.3. presents the exposure (mg/kd/day) and risk (MOE) estimates from all three models when food and Florida groundwater exposures are cumulated. At the upper percentiles presented the exposure from water overwhelms the food exposure. For all age groups the food plus water exposure is essentially the same as water exposure.

Table I.G.3. Estimated Exposures and Risk from Food and Water Combined

	95th Percentile		99th Percentile		99.9th Percentile	
Model	**Exp**	**MOE**	**Exp**	**MOE**	**Exp**	**MOE**
Infants < 1 years old						
DEEM/Calendex	0.008163	17	0.013529	10	0.022153	6
CARES	0.007873	18	0.013180	11	0.020710	7
Lifeline	0.006571	21	0.009441	15	0.012630	11
1 to 2 yr olds						
DEEM/Calendex	0.003497	40	0.006154	23	0.010839	13
CARES	0.003177	44	0.005462	26	0.009431	15
Lifeline	0.003765	37	0.006654	21	0.010329	14
3 to 5 yr olds						
DEEM/Calendex	0.003208	44	0.005686	25	0.010393	13
CARES	0.003133	45	0.005403	26	0.009033	15
Lifeline	0.003112	45	0.005621	25	0.008340	17
20 to 49 yr olds						
DEEM/Calendex	0.002048	68	0.003551	39	0.006958	20
CARES	0.002091	67	0.003338	42	0.006757	21
Lifeline	0.001558	90	0.003015	46	0.005438	26

* Exposures are in mg/kg/day in oxamyl equivalents

4. Comparison of DEEM/Calendex and CARES Exposure and Risk Estimates for Selected Residential Scenarios

For comparison of residential modeled results, the Agency chose three post application exposure scenarios for children, lawn care, pet collars, and indoor crack and crevice spray scenarios. These were selected due to their higher exposure relative to other residential scenarios.

Residential analysis with probabilistic models is more complex than dietary and water exposure analysis. The Agency continues to improve and fine tune its inputs and methods for Residential exposure estimation with both the Calendex and CARES models. In particular the Agency is rapidly improving its experience and estimation technique with the much newer CARES. All three residential scenarios are loaded and working in CARES. The Agency is analyzing the initial residential outputs from CARES and hopes to present the results in the next revision of this document.

The Agency has yet to complete a NMC residential analysis with the LifeLine model. Residential runs are far more complex to setup and run than the food and water modulus and the LifeLine model is the least compatible of the three models with the Agencies standard residential inputs.

H. Risk Characterization

1. Introduction

Risk estimates were presented as a temporal profile plot of margins of exposure (MOEs) over a period of 365 days in Section F of this document and its associated appendices. Various exposure pathways (e.g., residential, food, water) and routes (oral, inhalation, and dermal) were graphed individually in that section. Age-specific group results were shown graphically according to the region/water scenario combinations selected.

The present chapter characterizes the risks identified as part of this preliminary *N*-methyl carbamate cumulative risk assessment. The intent is to note and discuss uncertainties in the hazard and exposure elements of risk estimates and to quantitatively, when possible, or qualitatively assess the potential impact of those uncertainties on the risk estimates. Risk characterization is particularly important for an assessment as complex as the NMC CRA. Many types of data derived from a variety of sources have been combined to produce estimates of risk from exposure to multiple NMCs in food, drinking water, or from residential use.

It is important to note that this is a preliminary assessment and interpretation of results needs to be done with care. For example, the current assessment does not incorporate extrapolation, uncertainty, and safety factors for the individual NMC pesticides. Although EPA incorporated previous or on-going risk mitigation measures put in place as a result of some single-chemical reregistration decisions, single chemical risk assessments for three NMCs (aldicarb, carbofuran, formetanate) are not yet complete. Risk reduction measures that may be taken for these pesticides in the future will be incorporated in subsequent CRAs, as appropriate. Furthermore, EPA has not reached a decision as to the percentile of distribution to be used for regulatory purposes. In short, interpretation of the risk estimates presented in this preliminary CRA depends upon the synthesis and processing of considerable additional information. Therefore, **no single value in the assessment should be used to independently arrive at the interpretation of the risk estimates or results.**

2. Hazard and Dose-Response Assessment

The hazard and dose-response assessment is presented in detail in section I.B and the associated appendices, II.B.1-6. Those sections a) outline the steps in developing the dose-response relationships for each pesticide and its capacity to inhibit ChE in rats; b) describe the data used in the assessment; c)

summarize the empirical dose-response modeling which provides the basis for the RPFs, PODs, and estimates of ChE inhibition half life; and d) provide the rationale for selecting oxamyl as the index chemical.

In the absence of a fully developed PBPK/PD model, EPA has applied the RPF method. This method relies on the assumption of simple dose addition and uses empirical curve fitting models to determine RPFs and PODs. Dose addition is EPA's default assumption in multi-chemical risk assessment when there is no evidence to the contrary (USEPA, 2000d). Dose addition is considered a reasonable assumption for risk assessment purposes, particularly at low, environmentally-relevant exposure levels. There is, however, some uncertainty associated with this assumption. In order to address this uncertainty, EPA has undertaken a series of mixture experiments. The first experiment involved a seven chemical mixture using a mixture whose composition which used BMD estimates to provide points of comparisons. The analysis of the results from the mixture is still preliminary. However, preliminary analysis suggests that, under the conditions in the study, brain ChE inhibition from these seven NMCs was dose additive.

An important part of cumulative hazard assessment is the determination of chemical potency. To assess potency, EPA has developed an empirical dose response model to describe the dose response curves for each NMC. The model described is the result of multiplying a dose-response model (USEPA, 2002b) and a time-course model. In the current assessment, this model has been successfully applied to brain and RBC ChE to estimate $BMD_{10}/BMDL_{10}$ ratios and half life to recovery. EPA used all of the available rat RBC and brain (whole or half) ChE data in its estimates of potency. The ChE data used for the oral route of exposure is quite extensive and, in general, of good quality for dose-response modeling. The dermal and inhalation data are less extensive. Dose-response modeling was used when sufficient response data were available from dermal and inhalation studies.

EPA has elected to use the brain ChE data as the basis for developing RPFs and PODs for use in the preliminary assessment. Brain ChE inhibition is an appropriate endpoint for use as an adverse effect because it reflects a response in a target tissue of concern that is relevant to humans. Brain ChE inhibition is an acknowledged adverse effect in both humans and in laboratory animals. Therefore, error due to the extrapolation between the response in a surrogate tissue (i.e., red blood cell and plasma) and a target tissue itself (brain) is eliminated. The data for the brain compartment also have more narrow confidence limits compared to those from the RBC compartment, suggesting that there is much less variability in this compartment.

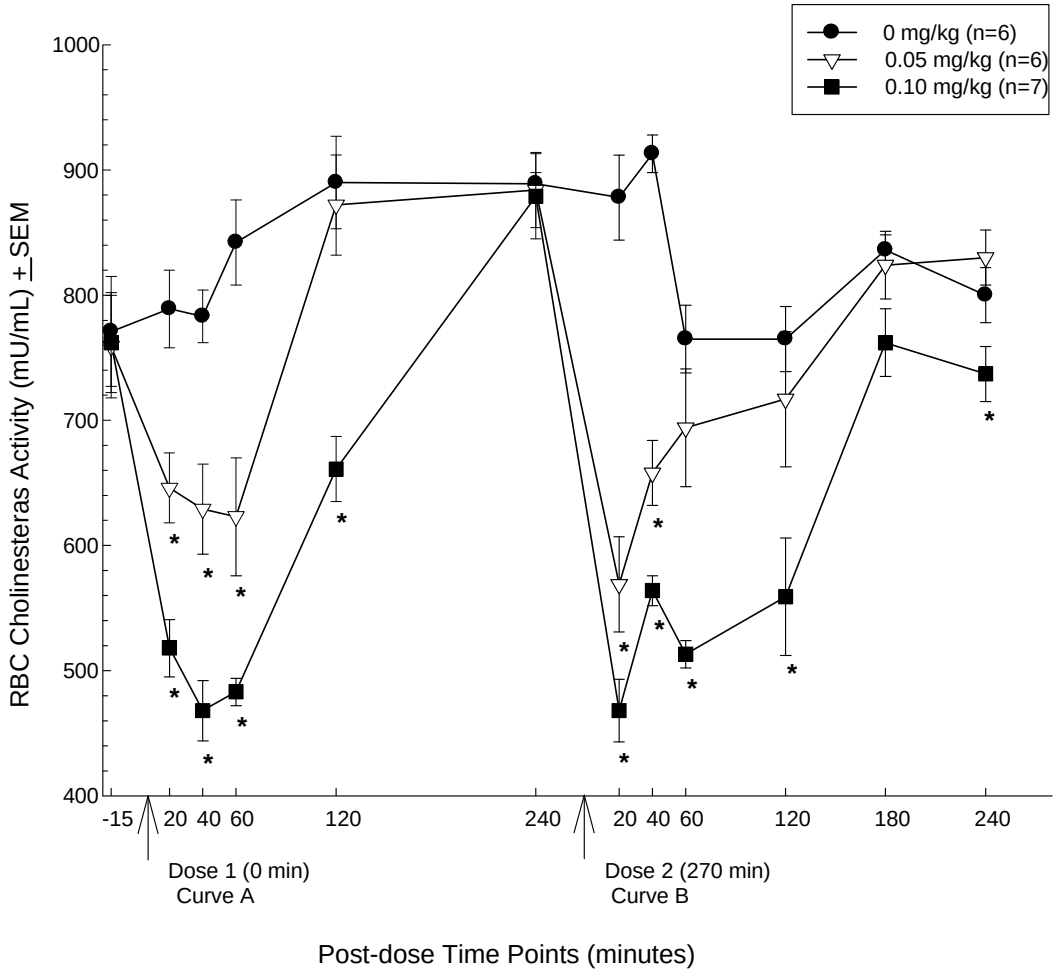
EPA selected oxamyl as the index chemical for the preliminary cumulative risk assessment. Oxamyl has sufficient data for cholinesterase inhibition to support modeling of a $BMD_{10}/BMDL_{10}$ by all three exposure routes of interest. The high quality dose response data for oxamyl permits reliable estimates of $BMDL_{10}$ which are being use as the PODs. Certainty in the PODs was

considered to be of great importance in as much as they are used to extrapolate cumulative risk.

Following maximal ChE inhibition, the rapid recovery observed with the NMCs is a unique characteristic of this common mechanism group. The rapid recovery observed following ChE inhibition with NMCs poses an additional challenge in the laboratory regarding the technique used to measure ChE inhibition. The radiometric method (Johnson and Russell, 1975) is the most appropriate method for measuring ChE for this group. However, use of a modified Ellman technique where controlled conditions such as temperature, time of assay, and dilution can be adapted to provide reliable measures of brain and RBC ChE inhibition. In the development of this preliminary cumulative risk assessment, EPA has assessed the quality of the ChE data by evaluating method descriptions from study reports, information made available by the pesticide registrants in laboratory protocols or Standard Operating Procedures, and gathered from EPA's own experiments. EPA believes that the rat toxicology studies in the current assessment provide reliable brain and RBC ChE data at or near peak ChE inhibition and for time to recovery.

EPA's current analysis suggests that time to half life of recovery for the NMCs range from a few minutes up to 12 hours, vary by chemical, and for some pesticides vary by dose. In EPA's dose-response analysis, ChE data from oral, gavage studies were evaluated. As noted in the I.B, EPA extracted data from several different study types. The important similarities among the design of these studies were that animals were dosed once a day by gavage and that ChE was measured at or near the peak time of effect. Most studies involved a single dose. However, for several NMCs (aldicarb, carbaryl, pirmicarb), subchronic, gavage studies were also available. These data were also extracted and statistically analyzed as part of the dose-response analysis. EPA's statistical tests for heterogeneity indicated that the BMDs did not vary with duration. These results suggest that following repeated single daily exposures did not lead to increasing levels of ChE inhibition. In a study by Tobia *et al*. (2001), cannulated rats were exposed to two oral doses of aldicarb spaced approximately 4.5 hours apart. As shown in Figure I.H.1 after the first dose, the ChE levels of aldicarb treated rats returned to levels similar to control animals by 4.5 hours post-dosing. After the second dose, the 0.05 mg/kg treated animals had ChE levels similar to control animals by three hours post-dosing. These results support EPA's assumption that the appropriate duration for the cumulative risk assessment for this class is acute exposure.

Figure I.H.1. Mean RBC ChE activity in cannulated adult male CD rats following a repeated oral administration of aldicarb
(Tobia *et al*, 2001; Reproduced with permission from author.)



*Significantly different from control within time point ($p<0.05$).

3. Recovery of ChE and Use of Calendex, CARES, and Lifeline Models

The use of DEEM/Calendex in conducting the current assessment and the results of the single pathway and cumulative assessments are described in previous sections of this document. Additional analyses were performed with CARES and Lifeline in order to compare results with those obtained from DEEM/Calendex. The comparisons are presented in section G of the document. All three of these models (DEEM/Calendex, CARES, and Lifeline) permit the simultaneous evaluation of more than one pathway of exposure which is a defining characteristic of aggregate and cumulative assessments. These models also permit the evaluation of exposure taking into consideration seasonal changes in exposure patterns as pest pressures change. Overall, the results of the three models compare well for the food pathway and food + water pathways. Additional comparisons of the residential exposure aspects of these models are ongoing. As was suggested by the SAP in earlier meetings, comparisons of model results consider only model uncertainty and simulation uncertainty. There are other significant aspects of uncertainty such as uncertainties associated with input variables that need to be explored. OPP intends to perform further analyses and comparisons for the revised version of this assessment as detailed in Section I of this document covering future activities and next steps.

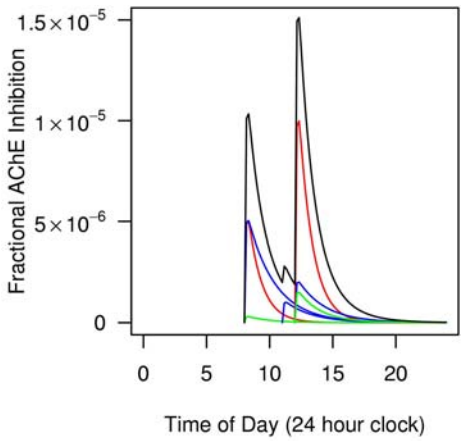
The DEEM/Calendex, Lifeline, and CARES models all use the Food Commodity Intake Database (FCID) to estimate food consumption. This database is derived, in part, from the consumption data from USDA's Continuing Survey of Food Intake by Individuals (CSFII). As described earlier, inhibition of ChE activity resulting from NMC exposure is rapidly reversible. Because this recovery occurs in minutes to hours, acute exposures are the relevant duration of exposure for these pesticides. With DEEM/Calendex, Lifeline, and CARES models, however, food exposures are summed over a 24-hour period and thus reflect daily (i.e., 24 hour) exposures[10]. This single-day (24 hour) mode of analysis used in this assessment does not attempt to reflect the characteristic recovery of ChE activity following inhibition by NMC pesticides.

Conceptually, a pharmacokinetic or biologically based model that accounts for the timing of environmental exposure(s) and the timing for ChE inhibition incorporates time to recovery for the individual chemicals would be available for evaluating the cumulative risk to the NMCs. EPA's on-going research efforts to build a PBPK/PD model for carbaryl and other NMCs are summarized in Appendix II.B.6. At the February, 2005 meeting of the FIFRA SAP, EPA presented a simple PK approach for evaluating ChE inhibition using basic assumptions about the quantitative nature of absorption, ChE inhibition, and recovery. At that time, EPA provided a simulated, hypothetical application of

[10] This summing over a 24 hour period is also true with all three models for both water and residential exposures. Thus, issues associated with these models not reflecting the characteristic recovery of AChE activity following inhibition by NMC pesticides extends to the drinking water and residential pathways as well.

this approach and received comments from the SAP on the basic assumptions and equations used. The results of this simulation are reproduced below in Figure I.H.2. Briefly, the red, blue, and green lines represent ChE inhibition following exposure to three simulated chemicals. The black line represents the cumulative ChE inhibition from all three. The spikes represent simulated, artificial exposure events which occur at different times. As described in more detail below, EPA's current exposure assessment may overestimate risk for some exposure scenarios due to limitations in existing probabilistic exposure models and existing drinking water consumption data. In the revised cumulative risk assessment for NMCs, EPA plans to perform simulations of NMC exposure using chemical specific data for ChE potency and recovery using this simple model. With this simple approach, the Agency can evaluate potential ChE inhibition from identified predicted exposure patterns or events. These simulations are expected to aid the Agency in its efforts to characterize ChE inhibition and recovery following NMC exposure, particularly from drinking water and residential exposures.

Figure I.H.2. Plot of simulation of pattern of ChE inhibition.



In the absence of a fully developed PBPK model and in the absence of probabilistic exposure models which can evaluate exposure durations shorter than 24 hours, OPP began an examination of the exposure patterns for food records from the high end of exposure distribution with the case study presented to the SAP in February, 2005. This exercise was an attempt at determining the degree to which high-end food exposures in the NMC CRA can be attributed to specific eating occasions (within a day) that occur closely spaced in time, occur widely separated by time, or come from single eating events by looking at actual individual eating occasions as recorded in the USDA's Continuing Survey of Food Intake by Individuals (CSFII) daily diaries. To the extent that a day's eating occasions leading to high total daily exposure are close together in time or occur from a single eating event such that minimal ChE recovery occurs between eating occasions (i.e., exposure events), the approach used in this Preliminary NMC assessment which sums eating events over a 24 hour period would provide reasonable estimates of risk from food. To the extent that eating occasions leading to high total daily exposures are widely separated in time such that substantial ChE recovery occurs between eating occasions, the estimated risks under the approach used in this Preliminary risk assessment may be overstated and a more sophisticated approach – one that accounts for intra-day eating patterns and the recovery of ChE between exposure events -- may be more appropriate. An analysis provided in the case study presented to the SAP in February 2005 indicates that daily exposures to NMC pesticides in the upper extremes of the distribution (99.8+ percentile) for exposures from food mainly involve single eating events. Specifically, OPP found that that a large fraction (~70%) of daily records contributing to the upper tail of the food exposure distribution represent single eating occasions (Figures I.H.3 & 4). The specifics associated with these analyses can be found in the NMC case study presented to the SAP in February 2005 (US EPA, 2005).

Figure I.H.3. Characterization of Food Exposure Children 3-5: number of eating occasions (sample of 8005 records from top 5 percentile exposure)

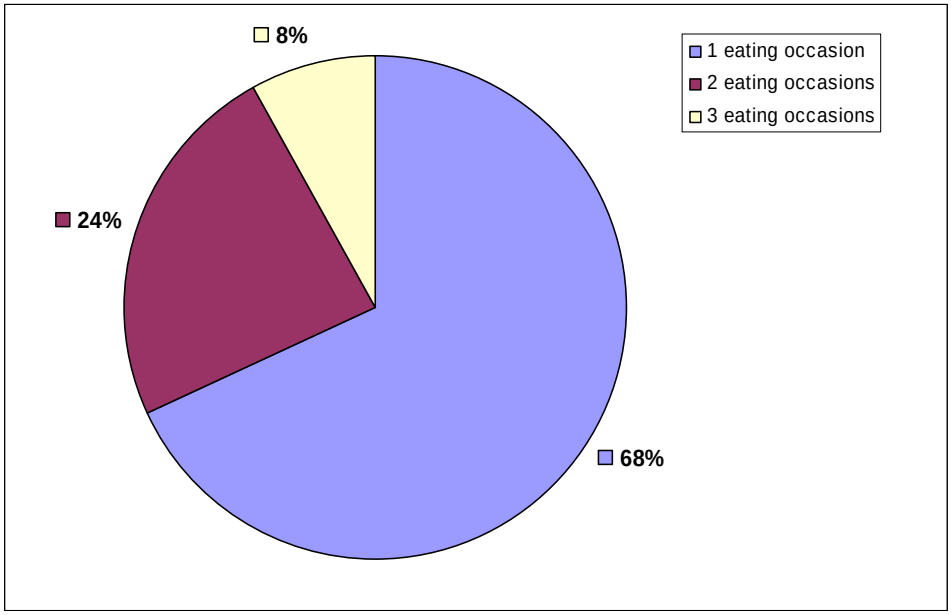
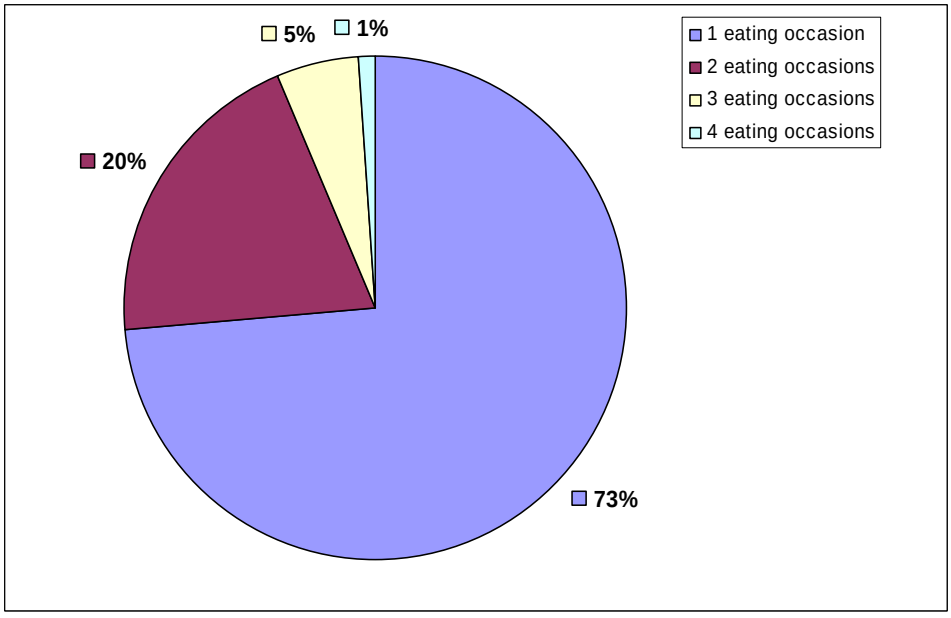


Figure I.H.4. Characterization of Food Exposure Children 3-5: number of eating occasions (sample of records near the 99.5th percentile)



Given that the large majority of daily, high-end food exposures to NMC pesticides appear to be associated with food intake at a single eating event during the day, OPP believes that it is unlikely that any more sophisticated, temporal-based approach which better accounts for temporal separation of eating/exposure events will result in substantial or significant changes in OPP's risk estimates associated with exposure through food. Thus, for food exposure when discussing the most highly exposed individuals, the issue of recovery times and their effect on those high-end exposures is likely to be of limited practical significance.

The analysis of food exposure patterns described above was possible, in part, due to the availability of high quality exposure data from the CSFII which includes daily timing of eating events. However, the CSFII does not include information regarding the consumption/exposure patterns for drinking water. Thus, as with the case of food, risks associated with exposure through the water pathway may be overestimated to the extent that consumption of water occurs throughout the day permitting at least partial recovery of ChE levels. The Agency is continuing to look for high-quality data which describes the pattern of drinking water consumption over the course of a day and thus is not able to quantitatively evaluate the extent to which risks associated with the water pathway may be overstated.

Reversibility was also not incorporated or considered for exposure/risks for post-application exposures from residential uses and post-application exposures. Exposures were assumed to occur on a single occasion. Exposure from dermal, inhalation, and oral routes of exposure vary substantially by age group, activity and patterns. When assessing inhalation from the crack and crevice use, EPA used a cumulative distribution up to 24 hours. However, for lawn exposure, children were assumed to have contact with treated lawns for up to 3.5 hours. Moreover, absorption kinetics differ significantly between dermal, inhalation, and oral exposures, further complicating recovery characterization.

In general, current limitations of existing databases and modeling software precludes quantitative consideration of <24 hour time periods. Because of this, a full characterization of the impact of recovery from exposure to NMCs from food, drinking water and/or residential exposures is not possible at this time. OPP believes that the food exposure assessment provides a reasonable estimation of risk. The drinking water and residential exposure assessment may overestimate exposure but the extent of this overestimation is not known. For the revised cumulative risk assessment, EPA will apply it's simple PK model to attempt to improve the characterization. As discussed during the February, 2005, SAP and also during the December 2004 SAP, OPP is cooperating with EPA's Office or Research and Development on work on a robust multi-chemical, multi-pathway pharmacokinetic model that will be able to incorporate finer temporal gradations of exposure through food, drinking water, and residential exposures.

4. Dietary Assessment

a. Use of CSFII Data

The NMC preliminary assessment is based on dietary consumption data obtained from the USDA's Continuing Survey of Food Intake by Individuals (CSFII) in years 1994-96/1998. This is an extensive two-part (1994-1996, and then 1998) survey and includes more than 20,000 individuals sampled over four years. The CSFII 1998, which supplements the 1994-96 survey data, added intake data from 5,560 children ages newborn through nine years of age to the intake data collected previously from 4,253 children of the same ages. This additional, supplemental children's survey was specifically requested of USDA by OPP in order to improve our ability to assess exposures to children. In each year of the survey, approximately 5,500 participants in 62 geographical areas across the country were interviewed on their dietary consumption over two separate (non-consecutive) days. The survey sample was scientifically selected so that the results could be projected from the sample to the U.S. population.

The survey design specifically required that survey data be collected from people who differ in ways that could affect the types and amounts of foods they eat. For example, the survey covers people of different ages, genders, ethnicity, regions of the country, and socioeconomic status. People who are selected for interviews are contacted on different days of the week, scattered throughout the year to capture differences due to the time of year or day of the week. A number of other aspects of the survey are also controlled in order to maximize the prospect that the results are representative not only of the entire U.S. population, but also particular subgroups, including those for which OPP generates acute dietary food exposure distributions.

While the USDA food consumption surveys are designed to be generally representative of the U.S. population, it is clear that some factors that can influence dietary choices are not addressed in the survey design. For example, the CSFII surveys do not purport to be representative of people in institutional living arrangements (colleges, nursing homes, etc.) or of different religions or health status. Specific subpopulations such as vegetarians, those on restricted diets, or those on specialized diets were not specifically surveyed. In addition, smaller specialized subpopulations such as Native Americans or subsistence fisherman, are not specifically targeted. Overall, however, the dietary information which OPP used as part of this preliminary cumulative assessment for the NMC is extensive, of high quality, and fully representative of many of the subgroups in the U.S. population. OPP is confident that the consumption data available from the CSFII 1994-96/1998 provide a reasonable basis for estimating exposure for the

subpopulations surveyed to NMCs in foods. OPP acknowledges that the use of CSFII in this assessment may not fully reflect the eating habits of high-end eaters or of specialized subpopulations which introduces some uncertainty with respect to the tails of the distribution of estimated exposures in the assessment. Nevertheless, OPP believes that the USDA CSFII reflects the best current nationally representative information available on food consumption in the U.S [11].

b. Use of PDP Data

USDA PDP data are used for most of the pesticide residues in food assessment. The use of PDP as a source of residue data has a number of inherent benefits that preclude the need for the use of conservative assumptions in the assessment. PDP provides a direct measure of the occurrence of more than one NMC in any sample analyzed. OPP can use these data as an indication of pesticide co-occurrence likely to be encountered in foods, and extrapolate accordingly. In other words, OPP assumes that co-occurrence of NMC residues in food throughout the U.S. mirrors the PDP values. In addition, PDP data reflects appropriately the use and usage practices that exist and this information is inherent in the data. Given the size, scope, and breath of the PDP data, little uncertainty is introduced by our use of this data.

In contrast to single chemical assessments, where non-detectable residues in food commodities are assumed to be present at one-half the limit of detection (LOD) of the analytical method, PDP samples with non-detectable residues are assumed to be "zero" values in this assessment. The impact of this assumption was tested in the original OP Cumulative Risk Case Study (USEPA, 2000c) that was presented to the SAP in December 2000. In this original OP Case Study, a similar use of PDP data as the residue data source in this assessment was demonstrated for 24 OPs. The resulting data set had characteristics very similar to the one used in the current assessment, and the analysis performed at that time demonstrated that the use of the "zero" values had only negligible impact on the MOEs developed at the upper percentiles of exposure. This is not unexpected: generally, the LODs for PDP data are very low (the average LOD for the entire data base is about 0.01 ppm) and the vast majority of exposures at the upper percentiles are derived from a single commodity and not a multitude of 1/ 2 LOD values. Therefore, it seems reasonable that the effect of assumptions related to estimation of values below the LOD would not significantly influence exposures at the highest percentiles of exposure. An analysis of this type for the NMCs is planned for the revised NMC assessment. To the extent that there is any effect, the use

[11] We note that the USDA has merged the CSFII Survey into NHANES (National Health and Nutrition and Examination Survey) and that future food consumption surveys will be derived from NHANES. OPP anticipates beginning to use the NHANES 99+ survey for food consumption sometime after the release of the revised cumulative assessment for the NMC pesticides.

of zero to reflect non-detectable PDP residues would tend to underestimate exposure and risk.

c. Data Translation from PDP

Not all foods to which the NMCs insecticides are applied are monitored in PDP. OPP has developed a scheme by which commodities that are measured by PDP serve as surrogate data sources for commodities that are not. This approach is outlined in OPP/HED SOP 99.3 (USEPA, 1999b). It is based upon the concept that families of commodities with similar cultural practices and insect pests are likely to have similar pesticide use patterns and similar residue concentrations. Although this assumption is generally sound, it introduces uncertainty with regard to how similar the use patterns for a given pesticide are to those for even closely related commodities. For example, the same NMC may be applied to different crops on a similar time schedule. However, the rates of application may differ between the crops treated. The number of treatments may also differ between the two crops. This issue is important to consider when conducting sensitivity analyses of the results of the risk assessment. When the data are adapted for the use of several chemicals simultaneously, and estimates of co-occurrence are derived from that data, the likelihood of an inappropriately assigned residue becomes greater. Although the commodities may have similar cultural practices, they may differ in the number of NMCs registered for these uses. In addition, the translation from one commodity to another implicitly assigns the inherent percent crop treated information from one commodity to another. The direction and magnitude of this error will be commodity-specific.

OPP believes that this potential source of error in its assessment will most likely result in some minor estimation bias. However, the magnitude of the error is not likely to be significant given that the commodities for which PDP data was translated represent only ~1% of a child's diet.

d. Other Sources of Residue Data

The PDP program provides pesticide residue data for a variety of fruits, vegetables, grains, beef, dairy products, pork, and chicken. Nevertheless, PDP data and surrogate PDP data do not cover all commodities of interest. For example, PDP does include data for seafood and eggs, so for these commodities, FDA's Total Diet Study and FDA Monitoring data were reviewed. Those data sources suggest that eggs and seafood contain negligible residues of the NMC, and LODs were very low. OPP thus used a zero to represent concentrations in these commodities. OPP considers this factor neutral with regard to the impact on the results of the assessment.

Approximately 3% of the foods consumed by children 1 - 2 years of age still remained unaccounted for after using FDA Total Diet Study and FDA Monitoring data. Sugar, molasses and syrups were assigned a residue value of zero. These products are highly processed commodities that are unlikely to retain any significant residues following the intensive processing procedures they undergo. The limited data from the Total Diet Study found no residues in pancake syrup or sugar.

Likewise, no data are available for field corn or dried beans. These commodities are also blended and highly processed before consumption. OPP believes that omission of these foods from the assessment will not result in an under-representation of exposure to NMC pesticides from food for children.

e. Impact of Risk Mitigation Actions

Inherent in the use of monitoring data to estimate future residues is the concern that past changes in use patterns will not be reflected in the current data set. With one exception (discussed below), the current preliminary NMC assessment includes all available years of usable data from PDP (1994 through 2003). To the extent that one or more NMCs are currently undergoing or may undergo future use changes as a result of the individual chemical decisions, OPP will consider this in the revised cumulative risk assessment for the NMCs. The one exception for which only the most recent PDP data was used was for formetanate HCl on oranges. For this crop/pesticide combination, there are large differences in the fraction of detectable residues and the associated concentrations between the years prior to label changes (e.g., 1994 and 1995) and years subsequent to label changes (e.g. 2001). This information was corroborated by information on use and usage practices by OPP's Biological and Economic Analysis Division. For these reasons, only the PDP data from years reflecting the newer labels and changed practices were used in this preliminary assessment.

We note that reregistration eligibility decisions have not been completed for all NMCs included in this assessment. Completion of the regulatory process for these pesticides could result in additional exposure and risk reduction measures. These changes could, in turn, result in further reductions in exposure in the food portion of the assessment. The magnitude of that change is uncertain.

5. Residential Assessment

The residential component of the preliminary NMC cumulative risk assessment is the second application of distributional analysis to residential exposure assessments that OPP has performed, the first example being the OP cumulative. In addition to incorporating distributional analysis, the assessment also factors in the seasonal and regional aspects of pesticide use. Three types of data are used in the residential assessment:

- Pesticide use,
- Pesticide residue dissipation, and
- Exposure contact/human exposure factors.

Pesticide use data are used to determine the percent of households using a pesticide, the timing of the pesticide treatments, and frequency and duration of exposure. In the current assessment, all pesticide use data are specific to the Southern regions of the U.S., such that residential exposure estimates reflect the long growing season and associated pest pressures of that area. All pesticide use data was based on pest pressures in the Southern region of the U.S. (specifically, Florida) Due to longer periods of pesticide use coupled with higher ground water concentrations, this assessment as a whole is assumed to provide a worst case estimate of exposure.

Pesticide residue dissipation data address the fate of the pesticides once applied to an environment (e.g., lawns). Exposure contact data are exposure-specific metrics that relate human exposure to pesticide residues. Humans come in contact with the residues by contacting the product directly or by contacting the residues left after the pesticide applications are made. Distributions of human exposure factors, such as the body weight assumption used in this assessment, come from the Agency Exposure Factors Handbook. These will not be discussed in the risk characterization of the document because the values are established and used throughout the Agency.

Each data set used in the assessment introduces possible uncertainties in the outcome of the exposure assessment. The majority of the most significant uncertainty appears to be related to post-application exposure from the lawn, indoor crack and crevice, and pet uses, particularly the non-dietary ingestion route for young children (1-6 years of age). A summary of these uncertainties, their direction and magnitude, is presented in Table I.H-1.

a. Pesticide Use Data

Accurate pesticide use data, including information on regional site/pest markets, timing of application and the percent of households using NMC products, are key to the residential risk assessment. In the absence of that specific pesticide use information, OPP developed

residential exposure scenarios based on timing aspects found in survey data from REJV, regional Cooperative Extension Service publications, and Doane's GolfTrak. While the REJV data contains a complete 12 month pesticide use diary for 1,217 household-users, use of these NMCs by homeowners is a relatively infrequent event, leading to relatively high uncertainty around the various pesticide use estimates. Additionally the REJV did not collect information on the purpose of use (pest treated), areas treated, or application rates. Therefore, REJV data was used in combination with professional judgment, product label information and pest pressure information from the Cooperative State Extension Services to estimate application frequency and timing. Doane's GolfTrak was used to identify the percent of golf courses treated with pesticides. OPP believes this is a robust data source.

b. Pesticide Residue and Exposure Contact Data

i. Dermal Exposure

Dermal exposure to pesticides may occur during application and post-application activities. Examples of application activities that might result in pesticide exposure include, are not limited to, spraying liquid pesticide formulations on ornamental plants, or applying granular formulations to residential turfgrass. Examples of post-application activities that might result in pesticide exposure include, but are not limited to, weeding and harvesting home gardens, mowing and playing on lawns, and playing golf. There are several post-application dermal exposure scenarios addressed in this assessment. These are: post application dermal exposure resulting from lawn care products, garden and home orchard products, crack and crevice products, pet collar products, and contact with treated golf courses.

The application of pesticides is one of the more straight-forward activity patterns to measure since it represents easily defined activities. As a result, exposure contact data used to assess exposures during application of consumer-oriented pesticides are the most robust information used in the residential portion of this assessment. Recent data generated by the Outdoor Residential Exposure Task Force (ORETF) have been used to assess the use of hose-end sprayers (lawn care products), rotary granular spreaders (lawn care products), hand-pump sprayers (home gardens and orchards) and hand held dusters (home vegetable gardens). Another study, submitted by a registrant, was also used to assess residential applicator exposure using granular shaker cans. All studies meet or exceed current Agency guideline requirements (in particular regarding the number of replicates) and can be extrapolated to include clothing scenarios ranging from

short-sleeved shirts and short pants to long-sleeved shirts and long pants. OPP has high confidence in the use of these data.

Like the applicator scenarios, the post application garden and home orchard exposure scenarios are easily defined activities. For harvesting vegetables or weeding, there is a substantial amount of data on farm worker exposures. These contact values have the potential to overestimate residential exposure, since they are based on activity patterns of individuals whose pay is based largely on their productivity. Professional harvesters are likely to be more efficient than most home gardeners, and therefore exposed to a greater amount of treated surface. Since home gardens consist of a wide variety of plants, the use of a uniform distribution of values represents activities as diverse as hoeing and harvesting. These values may overestimate early season activities that consist predominantly of potential exposure to small plants.

Dermal exposure from post-application contact with the lawn chemicals is equally varied. Contact data, representative of the range of human activities on lawns has been difficult to model. Dermal contact exposure values were identified for adults who performed scripted activities (Vaccaro et al., 1993) and for children performing non scripted activities (Black, 1993) on lawns treated with a non-toxic substance. Rates of transfer in the studies with surrogate compounds were similar to those observed in the chemical specific dissipation data available to OPP.

Turf transferable residue (TTR) data are available for carbaryl, the only chemical registered for residential lawn use considered in this assessment, but only for the liquid formulation. That data provides a conservative estimate of transferable residues associated with the granular formulation.[12] The use of liquid TTR will result in higher exposure than that of granular and therefore provides a conservative assessment of risk resulting from the lawn uses of carbaryl.

The current assessment also addresses dermal post-application exposure for adults and teens playing rounds of golf on treated courses. The liquid TTR data used to assess post-application exposure for the lawn care scenario was also used to assess risk for this scenario. Since golf course turf are intensively

[12] As noted earlier, the label of the liquid formulation is being modified as part of mitigation activities to permit only spot treatment uses (up to 1000 square feet); the liquid formulation will no longer be permitted for broadcast use (entire lawn) by homeowners. However, current TTR data only exist for the liquid formulation and these data were the data used for this assessment for both broadcast and spot treatment. Since TTR associated with the liquid formulation is expected to be higher than that associated with granular application, this is a conservative assumption that is expected to over-estimate exposure and associated risk.

maintained (watered and mowed every day), this residue data is assumed to overestimate residues on treated golf course turf. The exposure contact factors used to estimate post-application dermal exposure are based on a few measurements from two studies that assessed golfer exposure. The exposure duration for individuals playing golf was assumed to be two to four hours per day, based on information obtained from a 1992 survey conducted by the Center for Golf Course Management. These assumptions are expected to adequately estimate potential exposure for golfers.

The preliminary NMC CRA also considered exposures through the use of flea collar products for carbaryl and propoxur. Estimates of exposure for these scenarios were developed using an approach similar to the one taken with the turf care products and rely on pet fur transferable residue data for carbaryl. The dermal contact factor(s) for post application exposure is based on a shampoo and groomer exposure study for carbaryl in which each groomer shampooed the dogs, picked them up wet to be placed in crates until all the dogs were shampooed. The dogs were then dried and groomed. These activities are likely to result in higher contact factors than intermittent contact with a pet wearing a collar and thus provide a conservative estimate of exposure.

To address exposure resulting from the crack and crevice uses of propoxur, OPP assumed continuous exposure to residues measured on hard surfaces in and around kitchens and bathrooms following an indoor crack and crevice treatment. To provide a conservative assessment of risk, this assessment used only total deposition measurements taken in the kitchen and bathroom for exposure assessments covering the entire time spent in the household. OPP assumes a higher residue removal efficiency for hard surfaces versus carpets/upholstery, as demonstrated by the Clothier et al. studies (1999a, b). Measurements collected in and around upholstered surfaces and carpets showed residues orders of magnitude lower. Also, the nature of crack and crevice treatments are likely to result in a lower potential for exposure since, according to use directions, applications are made to areas that are less accessible (behind appliances and cabinets) than for typical broadcast treatments. In addition, the assumption of continuous exposure to these residues is likely to result in exaggerated exposure estimates.

Likewise, the non-dietary ingestion exposure estimates are also influenced by similar assumptions. It should be noted that this aspect of estimating non-dietary ingestion is problematic for all post application exposure scenarios (lawn, pet and crack and crevice) as noted below.

ii. Non-dietary ingestion

The majority of residential scenarios modeled for the CRA result in conservative estimates of exposure. Risk estimates for non-dietary oral exposure result in the lowest MOEs, and are therefore of greatest concern to the Agency. However, these low MOEs appear to result from incorporation of micro-activity data into our macro activity models. As a result, the non-dietary ingestion scenarios are the least refined exposure estimates.

The micro activity data used in this assessment include observational data of children's mouthing behavior. The frequency of hand-to-mouth events and other hand contact events (i.e., clothing, various surfaces, or nothing between events) evaluated in these observational studies were used to determine the frequency distributions described in the Preliminary NMC CRA. Estimates of the surface area mouthed were also estimated from the video data. When calculating non-dietary exposure, the model has the potential to select a single high percentile mouthing frequency and a single high percentile surface area mouthed for the entire exposure event (i.e., up to 8 hours for crack and crevice use). That is, the model assumes that, for each daily contact, the same surface of the contaminated hand will go into the mouth. In these cases, the model does not account for instances when contacts is with a small portion of the hand. Also, implicit in all hand to mouth exposure estimates, is the constant replenishment of residues on the hands between each mouthing event. However, it is unlikely that replenishment occurs between each contact. For instance, if a child contacts untreated surface after touching a treated surface, a portion of the initial residue will be transferred to the untreated surface and therefore not available for transfer to the mouth during a subsequent mouthing event.

In summary, for a given duration, the model may link upper percentile frequency variables with upper percentile surface areas contacted. Combining these factors with the assumption of total residue replenishment may mask the dynamic nature of mouthing behavior (i.e., high number of contacts with a small portion of the hand versus small number of contacts with a large area of the hand). The contact frequency and surface area data used in this assessment are taken from observational studies in which all hand contacts were recorded as hand-to-mouth events. While using this type of observational data is suitable to estimate non-dietary exposure as a series of micro activities, OPP realizes that this data may not be appropriate for the macro activity approach used in this assessment. However, this data is considered the best available at this time. OPP is involved in an upcoming workshop with ORD that will address this issue. Pending the outcome of this workshop and

the completion of EPA's Child Exposure Factor Handbook, the input variables for mouthing frequency and surface area may be changed in the revised NMC CRA.

Table I.H.1. Input Parameters Used in the Exposure Models: Bias, Assumptions, Uncertainties, and Strengths

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway	Human Activity Pattern	+ = upward ~ = neutral - = downward	
Lawn Exposure	Unit Exposure:push-type rotary spreader (mg exposure per amount of active ingredient applied)	+	Assumptions/Uncertainties 1. This unit exposure value is based on 30 replicates consisting of individuals using a push-type rotary spreader. A number of clothing scenarios are possible to be generated from these data. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 2. A lognormal distribution was selected. 3. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves and thus this may overestimate exposure for these residential handlers.. However, because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. 4. The surrogate compound (dacthal) used in the exposure study may be dustier than the granular formulations of the NMC compounds assessed. This factor increases confidence that this variable will not underestimate exposure.

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway	Human Activity Pattern	+ = upward ~ = neutral - = downward	
	Area treated (square feet)	- to ~	Assumptions/Uncertainties 5. A difficult variable to estimate. However, the assumption is reasonable given the application equipment used. Although, may underestimate areas that have larger lawns (midwest), margins of exposure are large.
	Dermal Contact Transfer	~ to +	6. Adults: activities performed with tank tops and short pants, lognormal distributions may be reflective of study design rather than actual activities (choreographed) 7. Children: Includes above scripted activities and a range of non scripted activities. Non-scripted activities lognormal distribution may be influenced by use of a non-toxic substance (not a pesticide) 8. Assumes all adults and children living in households being treated with lawn care products are exposed (enter treated area).
	Turf Residues: dermal and hand-to-mouth	+	9. Chemical specific data for liquid formulation of carbaryl. OPP expects this assumption to overestimate exposure to broadcast granular applications. Liquid applications provide more thorough coverage of turfgrass and therefore, likely result in greater exposure.
	Frequency of hand-to-mouth events and surface area of hand mouthed	+	10. Assume continuous hand replenishment for long durations. Also, high percentile frequency values coupled with large surface areas may produce unlikely estimates.

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway	Human Activity Pattern	+ = upward ~ = neutral - = downward	
	Duration on lawn	+	11. For children, the value used actually measured time spent outdoors and not just time spent on lawns. Does not account for survey responses of individuals that did not play on lawns or go outside.
Home Garden, Fruit Trees, and Ornamental Plants	Applicator: Hose-End Sprayer, Dust Shaker Can, Trigger Pump Sprayer, Handwand	~ to +	12. All UE data for these scenarios are chemical-specific. In this assessment short-sleeved shirt and short pants were assumed. This may overestimate exposure as large portion of exposure is to the lower legs and upper arms. Although a surrogate compound was used, exposure is believed to be more influenced by the type of equipment used rather being chemical specific. OPP has high confidence in these data. 13. A lognormal distribution was selected. 14. Assumed gloves are not worn. Survey data do indicate that some residential handlers use gloves. Because consumers are unlikely to use, remove and care for PPE in the manner of professionals, it is unclear what impact this may have on actual use. confidence in these data
	Area treated: ornamentals	~ to +	15. Assumes all plants are treated around the perimeter of an average-sized house.
	Area treated: vegetables	~	16. A lognormal distribution of a well studied variable.
	Area treated: fruit trees	+	17. Assumes all fruit trees are treated. Little data to determine actual area occupied by home orchard .

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway	Human Activity Pattern	+ = upward ~ = neutral - = downward	
	Postapplication: vegetables/fruits	~ to +	18. Contact values represent a wide range of activities. All plants are assumed to be treated.
	Postapplication: fruit trees	~ to +	19. Based on olive pruning study data.
	Plant residues	~	20. Based on chemical specific DFR data.
Ornamental Snail/Slug Bait	Applicator: Granular	~ to +	21. This unit exposure is based on 15 replicates. Chemical specific data. Used study assessing exposure while treating shrubs which had higher unit exposures than for flowers. 22. A lognormal distribution was selected.
Indoor Crack and Crevice	Applicator: Aerosol Can	+	23. Chemical specific applicator data, highest values used.
	Post-application: Residues and Air Concentrations	+	24. Chemical specific deposition data. Assume high removal due to hard surfaces.
	Post-application: Frequency of hand-to-mouth events and surface area of hand mouthed	+	25. Assume continuous hand replenishment for long durations. Also, high percentile frequency values coupled with large surface areas may produce unlikely estimates.
		+	26. Use of Exposure Factors Handbook breathing rates for light to moderate activities for inhalation duration. Assumed 8 hours of exposure per day for dermal and hand-to-mouth exposures. The 8-hour estimate is based on average number of hours children are awake each day; It does not account for time spent eating, bathing, or time spent outside of the home.

Duration

Model	Input Parameter	Bias*	Assumptions, Uncertainties, or Strengths and Other Comments
Exposure Model for Residential Pathway	Human Activity Pattern	+ = upward ~ = neutral - = downward	
Pet Collars	Postapplication	+	27. Dermal contact value, from studies in which there was substantial contact. 28. Chemical specific fur residue data. 29. Assume continuous hand replenishment for long durations. Also, high percentile frequency values coupled with large surface areas may produce unlikely estimates.
		+	30. Use of time spent performing animal care (feeding, walking). The duration assumes continuous contact rather than intermittent contact.
Golf	Post-application: Dermal Contact Transfer	~ to +	31. The surrogate data used to derive transfer coefficients were based on two measurements of four individuals playing golf on two golf courses treated with chlorothalonil (Ballee, 1990), and the exposure of golfers (four volunteers) to flurprimidol (Moran et al., 1987).
Duration		~	32. Estimate based on 1992 Golf Course Management Report, describing amount of time spent golfing.
	Turf Residues: dermal	+	33. Chemical specific data for liquid formulation of carbaryl.

Duration

6. Characterization of Drinking Water Exposures

The regional drinking water exposure assessments are intended to represent exposures from vulnerable drinking water sources resulting from typical carbamate usage. Each regional assessment focuses on areas where combined carbamate exposure is likely to be among the highest within the region as a result of total carbamate usage, adjusted for relative potencies, and vulnerability of the drinking water sources. For ground water, shallow private wells in highly permeable soil and vadose zone materials are expected to be most vulnerable. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable.

For most of the country, NMC residues in drinking water sources are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure (see Section I.D). However, NMC residues estimated for vulnerable private wells in some areas of Florida (primarily along the central ridge) and the southeastern coastal plain are major contributors to the cumulative NMC exposures. The estimated ground water concentrations are not national numbers but are reasonable for people living in those vulnerable areas who get their drinking water from shallow private wells. Further modeling for other areas will provide spatially-explicit estimates for populations drinking water from less-vulnerable ground water sources. Based on the regional assessments, NMC residues in surface water sources of drinking water are not expected to result in significant exposures.

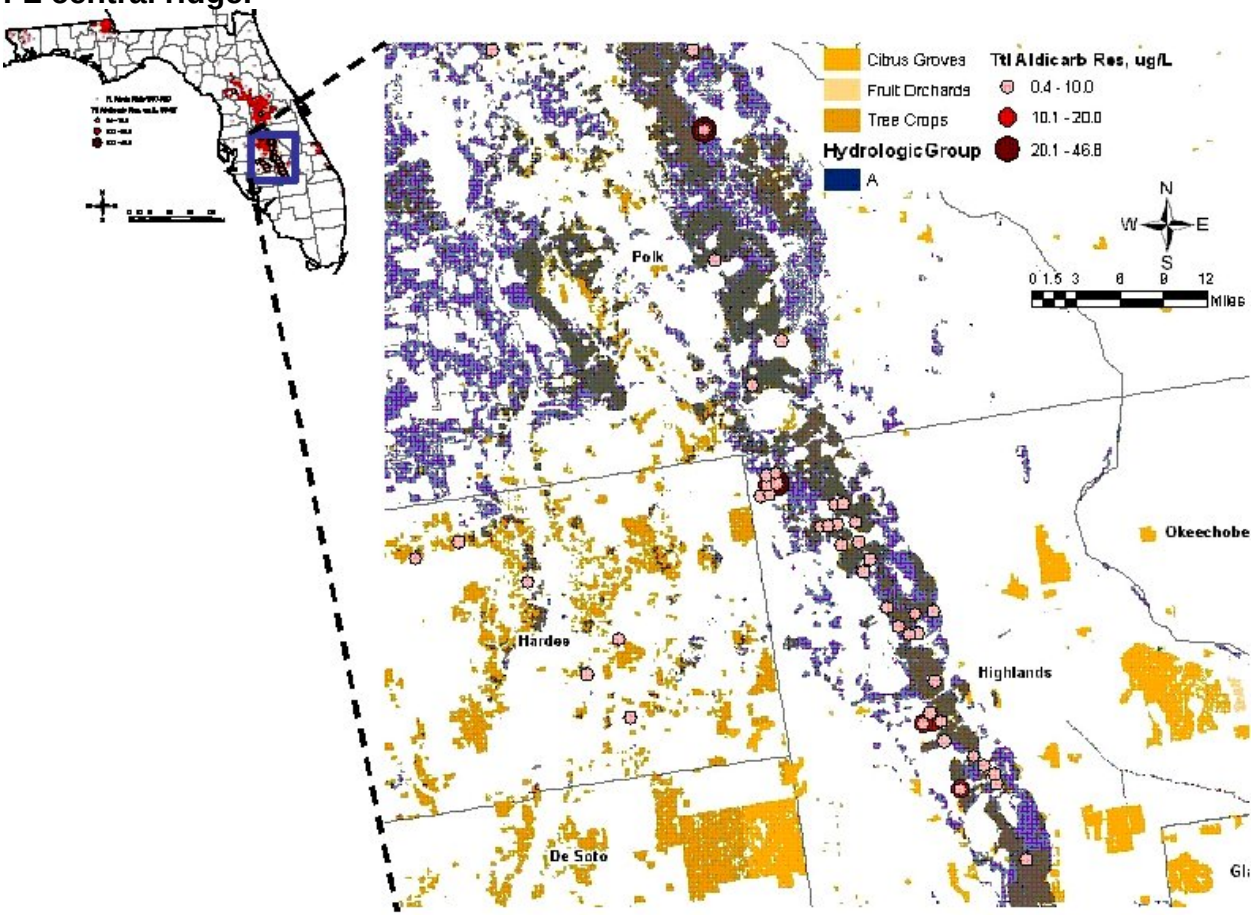
Because the selection process took into account the relative potencies of the carbamates pesticides, the sites used for the initial drinking water exposure estimates are biased toward the areas in which the more toxic carbamates are used. In particular, the regional cumulative sites tend to occur in areas of high aldicarb use (highest relative potency factor of 3.32). Since the purpose of the assessment is to identify the impact from multiple carbamates occurring in water in the same area, the area(s) selected for the assessment do not necessarily represent the highest exposure of a single chemical, but rather the highest multiple carbamate exposure within the region. Since pesticide use may vary from year to year and cropping and usage patterns may change, some areas in other parts of the region may have greater water exposure in a given year.

a. Ground Water Exposure

Based on available monitoring data and model projections, the Agency believes that the highest overall cumulative NMC concentrations in drinking water sources are from vulnerable private wells in citrus areas of the central ridge of Florida. The associated estimates derived from RZWQM, PRZM, and LEACHP models reflect a limited area where high carbamate use on citrus coincides with highly-permeable soils and shallow ground water (Figure I.H.5). Estimated NMC exposure in other carbamate use areas underlain by less permeable soils is expected to be considerably lower. Indeed, Figure I.H.5 shows other citrus areas where

NMC pesticides likely to be used but have no history of detections in private wells.

Figure I.H.5. Map showing overlap between citrus areas (orange) and highly permeable soils (blue) identifying vulnerable ground water areas (dark colors) in FL central ridge.



Similar conditions may occur in limited areas of the southeast coastal plain, represented by the eastern North Carolina and southwestern Georgia scenarios. However, the Agency doesn't have similarly comprehensive well monitoring in these areas. The Agency is compiling geographic coverages of vulnerable soils in the southeastern coastal plain and Florida to better define the extent of potentially vulnerable areas for the revised NMC CRA.

Assuming similar setbacks between treated areas and wells in other regions, the estimated NMC cumulative exposure in private wells in these areas is likely to be from 3 to 10 times lower in the southeastern coastal plain than in the central ridge of Florida. However, the most restrictive well setbacks apply only to aldicarb use on citrus in Florida. Since less-restrictive well setbacks are required for aldicarb in other parts of the country and given that aldicarb is the dominant carbamate used in the vulnerable areas of the southeastern coastal plain, the NMC

concentrations estimated for the coastal plain could be as high as those reported for Florida.

These concentrations represent the likely most vulnerable drinking water supplies in the regions: private wells drawing water from shallow, unconfined aquifers. The soil and vadose zone materials are highly permeable, allowing for a relatively rapid movement of pesticide and transformation product from the surface to the ground water. Because NMC residues are subject to pH-dependent hydrolysis, they will be more persistent in acidic soils and ground water than in neutral to alkaline soils and water. While only a few recent ground water monitoring studies exist to compare to model estimates, this assessment of vulnerable conditions is supported by historical monitoring data and label history for several of the NMC pesticides, particularly aldicarb and carbofuran. High concentrations of these pesticides (including both the parent pesticide and degradation products) have been found in wells across the country where the pesticide use coincided with highly permeable soils, shallow ground water, and acidic conditions (summarized in Section I.D). These detections led to voluntary label changes that restricted the use of those pesticides in some regions or placed conditions under which the pesticides could be used in some soils.

Actual NMC concentrations in private wells may vary from the estimated concentrations as a result of a number of factors. Important conditions that may affect NMC residue levels in drinking water from private wells include:

- **Depth to ground water:** The conceptual model set the top of the water table at 3.5 meters (12 feet) and the screening depth to 4.5 meters (15 feet). While ground water in Florida, the southeastern coastal plain, and other parts of the country may be found at this depth or shallower, few drinking water wells are expected to be shallower, and many will likely extend deeper. With deeper wells, travel time between the soil surface and ground water will increase, allowing more time for degradation in transit and lower concentrations.

- **Hydraulic conductivity of the soil/vadose zone:** The soils in the central ridge of Florida had very high saturated hydraulic conductivities. Less permeable soils and soils without substantial macropore flow are likely to result in lower than predicted concentrations because of the longer transport time.

- **Setback distances between the well and the treated field:** The Agency assumed a setback between the well and treated field of 1000 feet for the preliminary assessment. This maximum setback is only required for aldicarb use on citrus in Florida. For other uses and in other parts of the country, the setback may be as little as 50

feet. The conceptual model accounted for setback distances by increasing the travel time between the treated field and the well. The estimated NMC residues may be greater than predicted from the North Carolina and Georgia sites where the distance between the well and the treated field are closer than 1000 feet. However, the Agency does not have any monitoring data in similarly vulnerable areas with which to judge estimated concentrations.

- **Soil/vadose zone and ground water pH:** All of the NMC pesticides, except for the parent aldicarb, are susceptible to pH-dependent hydrolysis. Under acidic conditions (low pH), these chemicals persist; under alkaline conditions (high pH), they degrade rapidly. The estimated concentrations reflect acidic conditions. Where soils and water are neutral to alkaline, the concentrations are expected to be lower than those estimated for the preliminary assessment.

- **Label changes and mitigation impacts on residue levels:** Label changes for aldicarb, a major contributor to the NMC residue levels in ground water, made in the mid- to late-1990's were intended to reduce the amount of total aldicarb residues reaching ground water in vulnerable areas. These included well setbacks and some water management changes. While the Agency addressed well setbacks in the conceptual model, it did not explicitly account for recommended water management changes on the label. As noted in Section I.D, while the private well monitoring data from FL DEP, which analyzed water from the tap rather than from the well, indicate a reduction in total aldicarb residues detected in later years, interpretation of these results has been confounded because the state of Florida has also been placing carbon filters on the taps of those homes with aldicarb detections in well water. The Agency continues to look for data that may assist it in better evaluating the impacts of label mitigation on NMC residues in water.

Additional uncertainties may be seen in differences in estimates from the three models used by the Agency (PRZM, RZWQM, and LEACHP). The models provided predicted concentrations that were similar on average, but short-term concentration differences among the models varied considerably. Some of these differences may due to differences in the way the models handle degradation-temperature relationships, evapotranspiration, and weather generation.

The ground water exposure represents private drinking water wells. The Agency assumed in this assessment that, in general, public water supplies supplied by ground water will typically draw from deeper aquifers and/or aquifers that have a relatively impermeable layer between the surface and the water supply. Such supplies are expected to be much less vulnerable to pesticide contamination. Public water supplies have a

higher probability of being treated, although conventional treatments processes are likely to result in little or no reduction of NMC residues in water. However, where lime softening, which will accelerate pH-dependent hydrolysis for all but parent aldicarb, or activated carbon filtration is used, some reduction in NMC residues between untreated and treated water may occur (Appendix II.D.3).

The Agency is taking these issues to the FIFRA SAP in August 2005 and will revise the NMC CRA based on feedback from the SAP and from public comments on this preliminary assessment.

b. Surface Water Exposure

The Agency does not expect cumulative NMC residues in surface water sources of drinking water to reach levels that will contribute substantially to the cumulative exposure. Estimated NMC levels in drinking water from the coastal plain of North Carolina were greater than predicted for any of the other regional surface water exposure sites. When the drinking water component was combined with the food and residential exposure routes in the cumulative assessment, the highest seasonal exposures from surface water sources of drinking water were approximately an order of magnitude less than those estimated for food or for the total carbamate exposure from all routes. For most of the year, predicted exposures from drinking water were much lower.

Estimated peak concentrations for the NMC pesticides were similar to (in the case of aldicarb, methomyl, and oxamyl residues) or less than (in the case of carbaryl and carbofuran residues) the maximum detections reported in the USGS NAWQA program. Estimated peak modeled concentrations were greater than reported detections from the USGS Reservoir Monitoring Study.

For the surface water sources of drinking water, OPP used PRZM/EXAMS to predict pesticide concentrations in a small reservoir. This modeling approach makes certain assumptions regarding the nature of the drinking water source, the watershed, and year-to-year variability.

The reservoir used for the exposure assessment is based on the specific geometry (watershed and reservoir size) of an actual reservoir (Shipman City) in the Midwestern US. As such, it is more representative of potential transport to similar drinking water sources in high rainfall areas such as the midwest and eastern U.S. than in the west.

PRZM is not a basin-scale model, but a field-scale model which estimates edge-of-field pesticide loads in runoff. It does not explicitly account for the relative contributions of each field to the reservoir. OPP used a cumulative adjustment factor (a combination of the regional percentage of the total watershed area in crops with carbamate uses and

the percentage of acres treated by each carbamate on each crop) to adjust the resulting reservoir concentrations calculated by EXAMS (see USEPA, 2000b, for assumptions involved in applying Percent Crop Area factors for drinking water assessments).

PRZM does not account for location in the watershed: all fields are assumed to be uniformly distributed within the watershed, with runoff going directly into the reservoir. Each crop use simulated in PRZM assumes that the entire area of the watershed planted in the crop consists of a single soil. In each of the regions, OPP used data from local soils on which the crops are grown. When possible, the soil selected for each scenario was a benchmark soil that was prone to runoff (classified as hydrologic group "C" or "D" soils). While an assessment using a single soil assumes that each part of the watershed will be equally vulnerable to runoff, areas of higher and lower runoff vulnerability will exist in an actual watershed.

Because the application rates, frequencies, and timing are held constant, the PRZM/ EXAMS simulations over multiple years evaluate the impact of the variability in precipitation on the amount of pesticide that reaches surface water. Because weather data spanning 30 years is available for many locations across the country, PRZM/ EXAMS can account for pesticide runoff from a wide range of weather patterns not otherwise possible with monitoring studies that span relatively few years. The age of the weather data (1961 to 1990) limits OPP's ability to compare of the modeling output to more recent monitoring data.

Weather data files for PRZM are available for weather stations across the country. The weather station nearest to the county or counties used for the simulations was chosen for the cumulative assessment. To the extent that precipitation in these counties over the period of record might have been greater or less than that recorded at the nearest weather station, runoff for that area may have been over- or underestimated by PRZM.

c. Usage Information

Typical application rates and frequencies for each carbamate pesticide on each crop were generated by taking the average (spanning multiple years) of agricultural chemical usage surveys. This assumes that all applications were made at this typical or average rate and that frequencies of applications were constant year to year. Using these typical application rates and frequencies may underestimate water concentrations in years when pest pressure is higher than in our reported years and may overestimate in years when lower amounts of pesticide are used. The usage data was generally not sufficient to conduct a probabilistic assessment over a distribution of actual application rates.

The Agency used typical application rates and acres treated for the NMC assessment because of a low likelihood that all of the NMC pesticides will be used at maximum rates on all of the crop acreage at the same time. In the case of citrus, which resulted in the highest estimated NMC residues in drinking water for this assessment (for private wells along the central ridge), the maximum label rate for aldicarb, the major contributor to total NMC residues, is 4.95 lb ai/A, while the typical rate used was 3.9 lb ai/A. Given that estimated ground water residues are expected to be proportional to the application rate, the total NMC residues for private wells in the central ridge of FL would be no more than 20 percent greater than that used in the exposure assessment. In the earlier organophosphate (OP) cumulative risk assessment, the agency compared cumulative OP concentrations in surface water estimated using the average application rates with those estimated using maximum label rates. Estimated peak exposures assuming maximum application rates for all pesticides ranged from no difference for the Florida region to 2 to 4 times greater in the Southeast and Mid-south Regions (USEPA, 2002b).

The typical application rates and percent acres treated are derived from state-level data and assume uniform use practices across the state. Indeed, an uneven distribution of application rates and percent acres treated is expected in response to differing pest pressures. This assumption will underestimate areas where pest pressures may dictate a higher percentage of acres treated in a given year; similarly, it will overestimate areas where low pest pressures will require fewer acre treatments.

d. Timing of Exposure

OPP used crop profiles and other relative crop production publications to establish a window for the application date of the pesticide on a particular crop. This window doesn't necessarily reflect the range over which a pesticide will be applied in a particular year, but captures the year-to-year variation in the application dates over time. Thus, in any given year, the timing of application may be clustered within a shorter time-frame than suggested by the application window. However, because of weather and other environmental factors, the timing of intensive pest pressure and/or pesticide application may vary across the window. Thus, while the time series estimated in the drinking water exposures show a definite time period of peak exposures for surface water sources, the actual time of that peak may vary by several weeks, depending on the size of the window of application. While a slight seasonal pattern in ground water residue levels is evident in the FL central ridge estimates, seasonal patterns in ground water is less of an issue for private wells.

The date of application can have an effect on the predicted concentrations generated by PRZM/EXAMS for surface water exposure, depending on how near in time the pesticide application coincides with

rainfall events in any given year. OPP evaluated the impact varying the dates of application across the application window on the OP cumulative distribution (US EPA, 2002b). The impact of varying dates of application was most evident at the extremes in the distributions. The ratio in maximum concentrations between the lowest and highest estimates was a factor of 5 to 6. For 99th and lower percentiles, the differences were not as dramatic, with the ratio between lowest and highest values generally two or less. This analysis only looked at the cumulative OP distribution and did not evaluate variations in individual chemical distributions. This analysis has not been conducted for the NMC cumulative.

In the absence of data to show otherwise, OPP assumed that all of the pesticide applied on a particular crop is done on the same date. While this may be an unreasonable assumption for a large watershed, it is not unrealistic for the size of the watershed or fields overlying shallow aquifers supplying private wells used in this assessment. This assumption may result in higher peaks for surface water, but similar overall average concentrations than if applications are spread out over time. The resulting estimate of exposure may result in a small overestimation bias in the results that will be greater in large than in small watersheds. Little change is expected for ground water.

7. Conclusions

The appropriate matching of the common mechanism toxic effect and the duration of exposure is an important principle in cumulative risk assessment. While a sophisticated model such a PBPK/PD model could be used to account for the dynamic nature of environmental exposure, ChE inhibition, and rapid recovery, the tools and data necessary to perform such an analysis are not yet available to EPA for performing a cumulative risk assessment. At present time, the probabilistic exposure models currently available sum exposures over a 24 hour period. This single-day (24 hour) mode of analysis used in this assessment does not attempt to quantitatively reflect the characteristic recovery of ChE activity following inhibition by NMC pesticides. It is, however, still important to characterize, at least qualitatively and to the extent possible, how rapid recovery may affect the risk estimates. EPA has performed analysis of eating occasions for the food exposure assessment and will continue to perform analyses using existing tools for other pathways such as drinking water and residential exposure.

The food component of the NMC cumulative risk assessment is considered to be highly refined and to provide reasonable estimates of the distribution of exposures across the U.S. The exposure estimates for food are based on residue monitoring data from the USDA's Pesticide Data Program, supplemented with information from the Food and Drug Administration (FDA) Surveillance Monitoring Programs and Total Diet Study. The PDP data provide a very reliable estimate of pesticide residues in the major children's foods. The food component is also based on reliable food consumption data from the USDA's Continuing Survey of Food Intakes by Individuals, 1994-1996/1998

(CSFII). The CSFII surveyed more than 20,000 individuals and provides a detailed representation of the food consumption patterns of the US public across all age groups, during all times of the year and across all 50 states. In the food exposure assessment, EPA has performed an analysis of the eating occasions and concluded that because a sizable fraction (i.e., > ca. 2/3) of daily records contributing to the upper tail of the food exposure distribution represent single eating occasions and the number of records with eating events of 3 or more make up a small fraction of high end exposure records, summing food exposures over a 24 hour period is not likely to significantly overestimate the cumulative risk to the food pathway. Thus, EPA has confidence that the distribution of risk estimates for food are not overpredicted and reasonably reflects risks to the U.S. population

Exposures in drinking water to individuals are incorporated into the cumulative exposure assessment on a regional- and source water-specific basis (i.e., ground water and surface water, by region). They are intended to represent exposures from vulnerable drinking water sources resulting from typical carbamate usage and reflect seasonal variations as well as regional variations in cropping and NMC use. Each regional assessment focuses on areas where combined carbamate exposure is likely to be among the highest within the region as a result of total carbamate usage adjusted for relative potencies and vulnerability of the drinking water sources. For ground water, shallow private wells in highly permeable soil and vadose zone materials are expected to be most vulnerable. For surface water, drinking water reservoirs in small, predominantly agricultural watersheds are likely to be most vulnerable. Monitoring data are used to corroborate the modeling results and have helped confirm locations of potentially vulnerable drinking water sources.

In most of the country, NMC residues in drinking water sources are at levels that are not likely to contribute substantially to the multi-pathway cumulative exposure. However, NMC residues estimated for vulnerable private wells in some areas of Florida (primarily along the central ridge) and the southeastern coastal plain of NC can be major contributors to the cumulative NMC exposures from all routes. These areas represent what the Agency believes to be the most vulnerable private well drinking water sources for the NMCs based on available monitoring, current use patterns, and known soil and hydrologic conditions. In those vulnerable areas, which represent a relatively small area of the country, the estimated ground water residues are reasonable estimates of drinking water exposure for residents who get their drinking water from shallow private wells. EPA believes that the predicted concentrations of NMCs, particularly aldicarb for vulnerable drinking water sources, are reasonable estimates for those vulnerable sites. It is important to note that drinking water exposure to the NMCs in the majority of the US does not reach the levels predicted and/or observed in the Florida Central Ridge and the NC Coastal Plain but are instead expected to be very low.

As was done with food, EPA's preliminary cumulative risk assessment has summed drinking water exposure over 24 hour periods. Robust data evaluating

patterns of drinking water exposure are not available for quantitative analysis. However, EPA believes that patterns vary significantly by individual since some may drink moderate or large amounts of liquid at a time and some may drink small amounts of liquids throughout the day. EPA plans to use its simple PK approach for estimating ChE inhibition to simulate potential drinking water behavior patters as part of the revised cumulative risk assessment. Exposure summations over 24 hours as is done by the exposure models currently available may overestimate exposure but the degree to which exposure is overestimated is not known at this time.

With respect to residential uses of the NMCs, there are three NMC chemicals with currently registered residential uses considered as part of this preliminary cumulative assessment. Several reliable data sources were used to define how pesticides are used, dissipation of pesticide residues, how people may come into contact with pesticides (e.g., via dermal or inhalation exposure), and the length of time people might be exposed based on certain activities (e.g., playing on a treated lawn). Like drinking water, the residential exposure assessment is conducted on a regional basis and focused on the South (where use practices are expected to result in higher exposures than the rest of the U.S.) and also reflects seasonal variations. In particular, for the three routes considered in the residential assessment, exposure from hand-to-mouth activity by children and through the dermal route appear to be the most significant contributors to risk from residential exposures. Specifically, risks associated with crack and crevice uses of propoxur and those associated with pet collar uses of propoxur and carbaryl are the uses which are estimated to contribute the most to residential exposures. However, EPA notes that there are significant conservatisms incorporated into the assessment of these exposures: a discussion of this data, how it was used, and why it likely overestimates risk is detailed in the risk characterization section. Briefly, however, the model combines for a given duration a variety of high end assumptions that, in reality, are not likely to be simultaneously experienced. The model's combining of upper percentile frequency variables, upper percentile contact surface variables, and an assumption of total residue replenishment between individual hand-to-mouth events may mask the dynamic nature of mouthing behavior (i.e., high number of contacts with a small portion of the hand versus small number of contacts with a large area of the hand). While using this type of observational data is suitable for estimating non-dietary exposure as a series of micro activities, OPP realizes that this data may not be particularly appropriate for the macro activity approach used in this assessment. EPA expects to revise this portion of the assessment in the upcoming revised cumulative risk assessment after considering any advice and suggestions provided by the SAP.

In addition to the risks associated with the individual pathways described above, EPA also presented risk estimates associated with dietary exposure to food + water. For the specific regions for which the assessment was performed, EPA believes that these estimates are reasonable. However, as noted above and earlier in the document, exposures through water are likely spread over a longer portion of the day which would permit some recovery of ChE inhibition.

Thus, we believe that actual MOEs in these regions are somewhat greater than those cited for food alone but less than those cited for food + water. For areas outside the Florida Central Ridge and NC Coastal Plain, exposures and risks are expected to be lower (i.e, higher MOEs).

EPA also evaluated total MOE's for all three pathways (food + water + residential) simultaneously. To the extent that exposures through water and exposures through residential activities occur over the course of a day (as opposed to over a short period of time) and to the extent that there are significant conservatisms associated with the crack and crevice and pet collar scenarios, these risks are likely to be overstated to some degree. As indicated earlier, EPA will be requesting advice from the SAP on how those scenarios which contribute most significantly to estimated risks may be refined.

It is important to note that this is a preliminary assessment and, interpretation of results needs to be done with care. The current assessment does not incorporate extrapolation, uncertainty, and safety factors for the individual NMC pesticides. Furthermore, EPA has not reached a decision as to the percentile of distribution to be used for regulatory purposes or the target MOE's which will be employed. In short, interpretation of the risk estimates presented in this preliminary CRA depends upon the synthesis and processing of a vast body of data on hazard and exposures and no single value in the assessment should be used to independently arrive at the interpretation of the risk estimates or results.

As more robust data and new or improved models become available, cumulative risk assessment methods and approaches are expected to continue to improve and evolve in the future. At the present time, EPA believes that the preliminary cumulative risk assessment for the NMCs represents the state of the science regarding existing hazard and exposure data and the models and approaches used. This assessment is very complicated as it includes the integration of many data sets and multiple models and evaluated overlapping exposures from multiple routes throughout the year. EPA expects to make revisions in the coming months based on comments from the public and from the FIFRA SAP meeting planned for August, 2005. EPA also expects to include decisions regarding extrapolation and safety factors in the revised cumulative risk assessment.

I. Future Actions/Next Steps

The preliminary NMC cumulative risk assessment provides a detailed picture of potential exposures to NMC pesticides. Details retained in the assessment are sufficient to evaluate the impact of the methods and assumptions on the results of the assessment. This process is particularly important for a cumulative NMC assessment because of its complexity and the extent of additional data compared to single-chemical assessments. It uses distributions of data in place of point estimates to the extent possible, and introduces new data sources, particularly in the residential portion of the assessment, and new exposure pathways that were not considered or included in the earlier OP CRA. Other changes in the assessment process also warrant further investigation. OPP has used the NMC cumulative risk assessment as a vehicle to introduce a number of advances in its risk assessment methodology. These changes are most evident in the drinking water (e.g., consideration of groundwater exposure) and residential components (inclusion of more statistical details and methodology regarding distribution selection etc.) The NMC assessment was also the first time that OPP staff used multiple models (CARES and Lifeline in addition to DEEM/Calendex) to perform the assessment. Therefore, OPP plans to carefully analyze the results of the preliminary assessment and address many of the issues in a subsequent revised cumulative risk assessment for the NMC pesticides.

At this point in the planning process, OPP has developed a set of planned follow up analyses that will be conducted to assist interpretation of the results of the preliminary analysis, and to prepare an NMC cumulative risk assessment appropriate for use in the regulatory decision-making process. These next steps and questions to be explored are listed below, categorized by the portion of the assessment that they address. Some of the activities are flagged as long-term activities. These activities are not necessary for completion of the NMC cumulative risk assessment, but will be pursued -- several in cooperation with ORD -- in the interest of improving OPP's and the Agency's risk assessment processes. As noted previously in this document, new information submitted during the comment period that will serve to improve the accuracy of the assessment will be incorporated into the assessment. Further risk mitigation on individual chemicals will be incorporated in the revised assessment.

1. Hazard Assessment

- ❑ Define the data that are needed to better characterize the toxicity of NMC degradates and treatment byproducts in water systems. Evaluate and summarize existing data.

- ❑ Long term: Research to develop and implement physiologically based pharmacokinetic [PBPK] models, which describe the time course disposition of chemicals and their metabolites, are well suited to provide more refined estimates of relative toxic potencies and points of departure for future cumulative risk assessment. OPP is currently working with the EPA's Office of Research and Development on the development and testing of such models for common mechanism pesticides.

- ❑ Long term: Pursue with ORD investigations on the interactions among simple mixtures of common mechanism pesticides to better understand the concept and application of dose additivity (particularly with respect to the NMC pesticides)

2. Food Exposure Assessment

- ❑ Detailed analysis of food exposure to identify major contributors to risk, identifying specific food-pesticide combinations.

- ❑ Conduct of a series of sensitivity analyses for input parameters that are most likely to impact the outcome of the assessment and determine their effects. This will include deletion of earlier years, investigation of the effects of PDP data translation protocols, evaluation of the etc.

- ❑ Further evaluation of the sensitivity of estimated exposures to values used for non-detects.

- ❑ Evaluation of the Carbamate Market Basket Residue Monitoring Study and its implications for cumulative risk assessment (particularly with respect to issue of single item vs. composite samples).

- ❑ Long-term: Investigate the effect of seasonal residues and consumption patterns on the cumulative assessment.

- ❑ Evaluate the tails of the food exposure distribution to verify that unusual consumption patterns are not inappropriately impacting on the results of the assessment.

3. Drinking Water Exposure Assessment

- ❑ Complete assessment on spatial extent of potentially vulnerable ground water sources of drinking water in southeast. This may include mapping land characteristics (drinking water sources, land use, soils, hydrology, pH of soil and water) that lead to vulnerable conditions, estimating exposures for less vulnerable areas, and linking to populations.

- ❑ Analysis of uncertainty around the drinking water exposure estimates resulting from estimates of major use inputs (application rates, area treated, dates of application).

- ❑ Further evaluation of monitoring data, particularly for ground water, to investigate the sensitivity of depth to ground water on exposure estimates.

- ❑ Long term: Further comparisons of the three leaching models (PRZM, RZWQM, and LEACHP) for use in drinking water exposure assessments. This includes working with model developers on improving the model interfaces and functions.

4. Residential Exposure Assessment

- ❑ Verify residential use patterns and exposure schedules for NMCs and incorporate new data as it becomes available. Consider other information sources (including survey information).

- ❑ Conduct a series of sensitivity analyses for input distributions and associated parameters for residential exposure scenarios to determine those most likely to impact the outcome of the assessment and the impact of these distribution and parameter selections on the estimated exposures. Investigate impact of truncation of these distributions.

- ❑ Continue development of parallel residential assessments for CARES, LifeLine, and SHEDS and cumulate with existing food + water scenarios for these models.

- ❑ Long-term: Investigate other data sources (e.g., CHADS) and literature publications to better assess <24 hour (i.e., intra-day) timing of residential exposure events.

- ❑ Long term: Develop better methods for using current data regarding defining the hand to mouth behavior of children in a variety of settings and for active and quiet play.

- ❑ Long-term: Continued development and evaluation of non-standard residential scenarios such as track-in, institutional scenarios, dermal/oral contact for children in garden scenarios, etc.

- ❑ Further investigation of co-occurrence issues associated with residential exposure scenarios and incorporation into the models.

5. Risk Assessment Methodology

- ❑ Evaluate NHANES III and 99^{+} biomonitoring data for NMC metabolites in urine to provide a frame of reference for the results of the current assessment. Evaluate and identify additional sources of biomonitoring data (e.g., journal literature, study reports) for comparison and evaluation with respect to model outputs.

- ❑ Evaluate the impact of the number of iterations run on the model output in the upper percentiles of the risk assessment.

- ❑ Long-term: Perform formal uncertainty analysis.

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