

US EPA ARCHIVE DOCUMENT

# Use of Pharmacokinetic Data to Refine Carbaryl Risk Estimates from Oral and Dermal Exposure

Presented To The FIFRA Scientific Advisory Panel By:  
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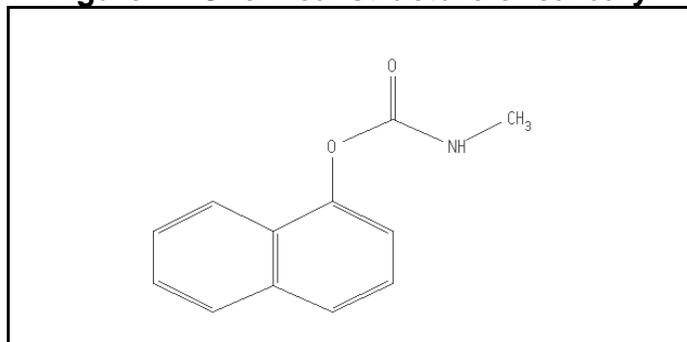
## Preface

The Food Quality Protection Act of 1996 requires EPA to reassess all previously approved pesticide tolerances by August, 2006. EPA issued the Interim Reregistration Eligibility Decision on June 30, 2003. That assessment is available at [http://www.epa.gov/oppsrrd1/REDS/carbaryl\\_ired.pdf](http://www.epa.gov/oppsrrd1/REDS/carbaryl_ired.pdf). On October 27, 2004, EPA published a Federal Register Notice (OPP-2003-0376). This Federal Register Notice indicated that Bayer CropScience, a registrant for technical carbaryl, had developed pharmacokinetic studies in rats to further evaluate the risk to children exposed to carbaryl following lawn treatment with liquid formulation. On December 2, 2004, the FIFRA Scientific Advisory Panel will hold a one-day meeting to consider the pharmacokinetic studies and extrapolation approach proposed by Bayer CropScience. This approach may provide a more refined method to estimating risk by the use of internal doses to calculate peak target tissue concentrations associated with the use of carbaryl, instead of administered dose, as typically used by EPA. The purpose of the current document is to briefly summarize background information regarding the metabolic profile for carbaryl, the animal pharmacokinetic studies, and the proposed extrapolation approach. More detailed information can be found in the documents developed by Bayer CropScience which are provided to the panel as appendices.

## 1. Introduction

Carbaryl is an N-methylcarbamate insecticide with many agricultural and residential uses, which include uses on lawns, gardens, and ornamental plants. The primary mode of toxic action for carbaryl is inhibition of acetylcholinesterase through carbamylation of the enzyme active site. This inhibition leads to accumulation of acetylcholine and results in cholinergic toxicity due to continuous stimulation of cholinergic receptors. The binding of carbaryl to acetylcholinesterase is rapidly reversible.

**Figure 1. Chemical structure of carbaryl**



The exposure of key concern is for young children who play on turf treated with carbaryl which can lead to oral and dermal exposures because of mouthing behaviors and physical contact with treated turf.

The endpoint for short-term incidental oral exposure was decreased cholinesterase activity (erythrocyte, whole blood, plasma, brain) and functional observational changes in a developmental neurotoxicity study in rats; the no-observed-adverse-effect-level (NOAEL) was 1 mg/kg/day and the lowest-observed-adverse-effect-level was 10 mg/kg/day. For short-term dermal exposure, the endpoint was decreased cholinesterase activity (erythrocyte and brain) in a 4-week dermal toxicity study in rats; the NOAEL was 20 mg/kg/day and the LOAEL was 50 mg/kg/day. The NOAELs from these two studies provide the 'low' dose in the carbaryl pharmacokinetic studies summarized below.

The Agency typically assesses human risks to pesticides by comparing the no-observed-adverse-effect-level (NOAEL) in lab animals to human exposures and calculating a margin-of-exposure (MOE):  $MOE = NOAEL/Dose$ .

The Bayer approach compares internal peak or plateau doses in the target tissue, brain, rather than the total absorbed dose. Because of the pharmacokinetic and pharmacodynamic characteristics of carbaryl, peak tissue concentrations of carbaryl resulting from oral exposure do not overlap the peak concentrations from dermal exposure. Also, peak or plateau tissue concentrations resulting from repeated oral exposure that reflect childrens' behavior should be lower than peak concentrations from a single bolus administration used in the laboratory studies.

In the Bayer proposal, a margin-of-exposure would be calculated by comparing peak brain concentrations of carbaryl determined after dosing rats in two studies. In one study, rats received an oral dose equivalent to the oral NOAEL. In the other study, rats received concurrent dermal and oral exposure at doses similar to those expected in a residential setting. In the mixed-dose study, rats received two oral bolus doses rather than twenty doses per hour assumed in children from residential exposure and the Bayer proposal included pharmacokinetic calculations extrapolating brain concentrations expected from twenty doses.

## 2. Use of Pharmacokinetic Data to Refine Carbaryl Exposure Estimates from Oral and Dermal Exposure

This document cites 2 recent Bayer metabolism studies, which for convenience, shall be referred to as:

- **Bayer metabolism study:** *Metabolism of [<sup>14</sup>C] Carbaryl in Rats*. Krolski, et al. Bayer CropScience. May 7, 2004. 230 pages. (Appendix 2)
- **Bayer mixed-dose study:** *Metabolism and Pharmacokinetics of [<sup>14</sup>C] Carbaryl in Rats Following Mixed Oral and Dermal Exposure*. Krolski, et al. Bayer CropScience. May 7, 2004. 53 pages. (Appendix 3)

### 2.1 Summary of Carbaryl Metabolism

The Bayer proposal to calculate a margin-of-exposure using peak target tissue concentrations is based upon these pharmacokinetic and pharmacodynamic characteristics: 1) oral absorption of carbaryl is rapid and complete; 2) dermal absorption is prolonged in comparison to oral absorption; 3) duration of binding to acetylcholinesterase is brief; 4) plasma half-life of carbaryl is short; and 5) metabolites are generally less toxic than parent carbaryl. Because of these characteristics, peak tissue concentrations of carbaryl resulting from oral exposure do not overlap peak concentrations from concurrent dermal exposure. Also, peak or plateau tissue concentrations resulting from repeated oral exposure should be lower than peak concentrations from a single bolus administration.

There are a number of studies characterizing rat and human metabolism of carbaryl. Although these studies were conducted for different time periods and used different analytical techniques, they showed that carbaryl metabolism is similar between rats and humans. Bayer's analysis focused on the alpha phase of kinetics, which is the first phase of the dose-response curve, because this is the time period of concern for children on treated lawns.

Oral absorption of carbaryl is rapid and essentially complete. The near complete absorption of carbaryl by the oral route is shown by comparing tissue concentrations after oral and intravenous (i.v.) exposure (Bayer metabolism study, Appendix 2). Tissue concentrations in the oral group of 1.08 mg/kg were

very comparable to those in an i.v. group of 0.80 mg/kg at the same time periods (Tables 1 and 2). The near complete absorption of carbaryl by the oral route is also shown by comparing excretion after administration by oral and i.v. routes. In a study in which rats received a single dose of 1 mg/kg/day by either oral or intravenous routes, both groups had 88-92% excretion of administered dose in urine and ~ 9% in feces (Struble).

Oral absorption of carbaryl occurs rapidly. Peak radioactivity in brain, plasma, whole blood, and red blood cells was reached by the first sampling period 15 minutes after rats received an oral dose of 1.08 mg/kg (Table 2).

Dermal absorption is both a slower process and less complete than oral absorption. For dermal exposure, peak radioactivity in the same tissues was not reached until 4 hours after a dose of 17.25 mg/kg. Peak tissue levels after a dermal dose of 17.25 mg/kg were approximately an order of magnitude less than peak tissue levels after an oral dose 1.08 mg/kg (Tables 2 and 3 in Appendix). The dermal absorption values from a guideline study were 5% for 2 hr exposure, 13% for 10 hr exposure, and 25% for 24 hr exposure (Cheng).

The duration of binding of carbaryl to cholinesterase is brief. Although the half-life of cholinesterase inhibition in rats was reported as 3.0 hours in the Bayer proposal, more recent calculations show the half-life is 1.7 hours (Brooks and Broxup). The half-life for cholinesterase inhibition in humans is 2.6 hours (May).

The elimination half-life of carbaryl is also short. The plasma half-life in humans after oral ingestion of 1.0 mg/kg carbaryl is 0.79 hours (May). The plasma half-life in rats for radioactivity in the alpha phase in the 2 recent Bayer metabolism studies varied somewhat depending on dose and route of exposure, but the plasma half-life after oral ingestion of 1.0 mg/kg carbaryl was 1.2 hours (Table 4 in Appendix). The half-life tended to decrease with decreasing dose.

Urine is the major route of excretion in rats and humans. Chromatograms of urine from rat and human studies were compared by one author (Knaak, 1965 and 1968) and with the exception of one metabolite, had the same peaks. 1-Naphthol is a major urinary metabolite in both rats and humans, accounting for approximately 40% of administered dose in rats and humans (Totis and Knaak, 1968).

Principal urinary metabolites identified in the guideline rat studies are free and conjugated naphthol and hydroxy carbaryl metabolites. Carbaryl metabolites are also excreted in bile and undergo extensive enterohepatic recirculation. Bile cannulated rats had 45% excretion in bile, 42% excretion in urine, and 1% in feces after oral administration of carbaryl (Marshall).

A biomonitoring study was conducted by Bayer to quantify exposure after application of carbaryl to residential lawns and gardens. Twenty-four hour composite urine samples were collected from each resident beginning 2 days

prior to application and ending 3 days after application. A carbaryl metabolite (1-naphthol) was used to calculate absorbed dose estimates for carbaryl. Carbaryl absorbed dose estimates were calculated from 1-naphthol levels using factors determined in an analysis of rat and human pharmacokinetic data. Many individuals potentially experienced multiple exposures as they re-entered lawns where carbaryl had been applied. The excretion profile indicated that it took approximately 96 hours for elimination and that approximately 50 percent was eliminated in the first 24 hours, which made calculation of absorbed dose estimates difficult because of the potential for multiple exposures (Carbaryl Revised HED Risk Assessment, March 14, 2003).

The following metabolites were identified in tissues in the recent metabolism studies performed by Bayer. Carbaryl *per se* was identified in brain, fat, liver; 1-naphthol was identified in brain, fat, liver, blood, plasma, RBC; the sulfate conjugate of 1-naphthol was identified in plasma; N-hydroxymethyl carbaryl was identified in brain. Low concentrations of carbaryl *per se* were found briefly in plasma after i.v. exposure, but carbaryl *per se* was not detected in plasma following oral or dermal exposure.

The Bayer proposal described carbaryl metabolism:

"When we look at the metabolic profile at "low" dosages, (more comparable to those experienced by humans), the predominant pathway is hydrolysis of the carbamate linkage, although there is a small and insignificant amount of oxidative metabolism on the ring while the carbamate linkage is intact. When we look at the metabolic profile at "low" dosages, (more comparable to those experienced by humans), the primary pathway is overwhelmingly hydrolytic. For example, at both the LOAEL and NOAEL in the rat (10 and 1 mg/kg, respectively), the primary metabolite seen at peak plasma concentration of total radiocarbon is 1-naphthol. The other carbaryl metabolites retaining the carbamate linkage (3 and 4-hydroxy carbaryl) represent a total of less than 1 % of the TRR in any tissue (Krolski et al., 2004a) and are also poorer cholinesterase inhibitors than carbaryl (Kuhr, 1971). Additionally, hydroxylated metabolites exist almost exclusively as their secondary metabolites (i.e., glucuronide and sulfate conjugates) that are much more water soluble and even less likely to interact with cholinesterase because of this water solubility and increased molecular bulk."

See Appendix 5, Proposed Metabolic Pathway in Rats (Struble)

## 2.2. Analysis of Bayer Mixed-dose Pharmacokinetic Studies in Rats

The Bayer pharmacokinetic proposal is based primarily upon a pharmacokinetic study in rats, referred to as the Bayer mixed-dose study (*Metabolism and Pharmacokinetics of [<sup>14</sup>C] Carbaryl in Rats Following Mixed Oral and Dermal Exposure*, Krolski, 2004, 53 pages - Appendix 3).

Doses in the Bayer mixed-dose study were selected to mimic exposure estimated for children playing on lawns treated with carbaryl. Children's exposure can include dermal exposure and oral exposure from mouthing behaviors. In the mixed-dose study, rats received concurrent dermal and oral exposure: rats were treated dermally for 2 hours with 0.871 mg/kg and received two oral doses of 0.0841 mg/kg at a 1-hour interval. Sacrifices were made 15 minutes, 30 minutes, 1 hour, 3 hours, and 5-hours following the second oral dose. Total radioactive residues were determined for whole blood, plasma, red blood cells, and brain. Metabolites were identified in plasma or brain when sufficient residue was present.

Total radioactive residue (TRR) in all tissues had peaked at the first sampling period, 15 minutes after the second oral dose (Table 5 and Figure 5 in Appendix). TRR in brain was 0.0206 ppm, of which 22% was carbaryl *per se*, 12% was 1-naphthol, and 12% was 1-naphthol sulfate (Table 6). By 5 hours, TRR had declined to 0.0043 ppm, of which 15% was carbaryl *per se*, 6% was 1-naphthol, and 19% was 1-naphthol sulfate. There was a slight increase in radioactivity in whole blood at the 1 hour sampling period, possibly due to dermal absorption.

## 2.3 Calculating Plateau Brain Concentrations After Divided Doses

Assumed oral exposure for a toddler is 20 exposures per hour for 2 hours, based on EPA's SOPs (*Agency's SOPs For Residential Exposure Assessment*). However, the dosing regimen used in the mixed-dose rat study was 2 oral doses given 1 hour apart. Because of carbaryl's short half-life, the 2 oral bolus doses resulted in much higher peak brain concentrations than would be expected to occur from 40 divided doses. Bayer therefore calculated the plateau brain concentrations which would result from 40 divided doses over a 2 hour period.

Each individual dose would be **0.00375 mg/kg** (0.15/40). The brain concentration at this dose was extrapolated, rather than determined in an experiment. Bayer's explanation for this regimen was:

"A single oral dose at 0.00375 mg/kg would yield brain concentrations several fold less than the lowest detection limit. Attempting to orally dose a rat 20 times per hour is extremely traumatic to the animal (which would affect the results and not be allowed by the American Association for Accreditation of Laboratory Animal Care), and would have required several people to dose four rats at this frequency resulting in additional experimental (interperson) uncertainty."

Bayer extrapolated the carbaryl concentration in brain from a dose of 0.00375 mg/kg using brain concentrations obtained following doses of 0.084 mg/kg, 1 mg/kg, and 10 mg/kg in the two Bayer studies. The extrapolated plateau brain concentration following a single dose of 0.00375 mg/kg was **0.000091 ppm** (pages 15 and 16, Bayer proposal).

The half-life of carbaryl in brain from the mixed-dose study was estimated to be **15 minutes** because carbaryl concentration declined from 0.0045 ppm to 0.0023 ppm between the 15 minute and 30 minute sampling periods and  $0.0023/0.0045 = 51\%$  (Table 6). The half-life of total radioactive residues (TRR) in brain from the mixed-dose study was estimated to be **19 minutes** because TRR declined from 0.0206 ppm to 0.0129 ppm between the 15 minute and 30 minute sampling periods (Table 5). Bayer reported: "The 30 minute concentration is 62.7% of the 15 minute concentration. The ratio of 62.7% to 50% is 1.25, which adjusts the 15 minute period to 19 minutes or 0.33 hours" (email, 10/12/04). Bayer reported that there was not a significant difference between 15 minute and 19 minute values, and the half-life of 19 minutes was used to estimate the plateau value.

Bayer next estimated the plateau brain concentration resulting from 40 oral exposures of 0.00375 mg/kg to be **0.0011 ppm** using the following equation and explanation excerpted from page 19 of the Bayer proposal. Calculations are shown on the attached spread sheet (Appendix4) (MOE\_Derivation\_HtM\_EPAScenario\_10Jun04.xls).

$$C_p = (C_{d\_event1} \times F) + (C_{d\_event2 \text{ thru } n} \times F)$$

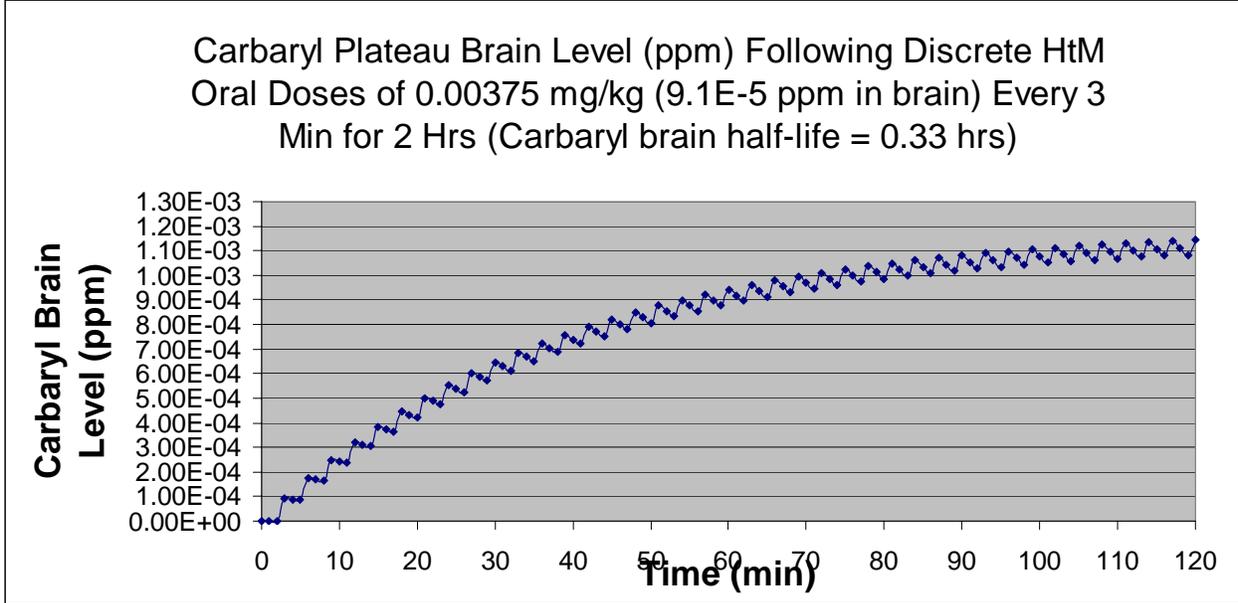
where  $C_p$  = carbaryl concentration (mg/mL or ppm) in the brain at plateau or peak;

$C_{d\_event1 \text{ thru } n}$  = concentration (mg/mL or ppm) in the brain (0.000091 ppm) at each incremental time step (min), where an oral dose of 0.00375 mg/kg occurs at a frequency of 20 events per hour or once every 3 minutes ( $0.00375 \text{ mg/kg} = 0.15 \text{ mg/kg/day} / 40 \text{ events per day}$ );

F = fraction of brain level eliminated at each time step (0.025 per min based on 0.5 in 0.33 hrs [the measured carbaryl half-life (hrs) in brain at 10 mg/kg following oral dosing was 0.30 hours and the estimated carbaryl half-life following first oral dose of 0.084 mg/kg and concurrent dermal dose of 0.871 mg/kg was 0.33 hours]).

Figure 2 shows that the extrapolated plateau brain concentration is reached after approximately 90 minutes. After that time, repeated exposures do not result in appreciable increases in brain concentration of carbaryl.

**Figure 2. Extrapolated Plateau Brain Concentration**



Adapted from Figure 3, page 19, Bayer proposal.

## 2.4. Extrapolation of Results From Mixed-dose Study to Biomonitoring Study

A second component of Bayer's proposal is to extrapolate peak internal doses from the mixed-dose study in rats to absorbed doses in the biomonitoring study. In the biomonitoring study (described above in Summary of carbaryl metabolism), total carbaryl absorbed dose was estimated after application of carbaryl in a residential setting. This absorbed dose in the biomonitoring study was estimated using urine concentrations of 1-naphthol in humans which were converted to absorbed carbaryl equivalents. The 1-naphthol to carbaryl conversion factor of 3.5 was determined from an analysis of human and rat pharmacokinetic data (Carbaryl Revised HED Risk Assessment, March 14, 2003). The urine samples were 24 hour composite samples collected on the day of application and each day for 3 days after application. Following carbaryl human exposure, carbaryl is rapidly metabolized and 1-Naphthol is excreted over a 96-hour period. EPA's risk assessment estimated exposure using two different approaches:

- Assuming total carbaryl dose values summed over a 96-hour period equals one daily dose
- Assuming total carbaryl dose values summed for a 24-hour period equals one daily dose

Bayer compared margins-of-exposure (MOEs) calculated in the manner in which EPA traditionally assesses exposure to the method in Section 2.3, above. In the carbaryl risk assessment, EPA determined an MOE of 4 by dividing the NOAEL for incidental oral exposure (1 mg/kg/day from the rat developmental neurotoxicity study) to the expected toddler exposure (0.25 mg/kg/day) determined from EPA's SOPs For Residential Exposure Assessment.

Bayer reported an MOE of 70 by dividing the peak brain concentration (0.077 ppm) in rats dosed at the oral NOAEL by extrapolated plateau brain concentrations (0.0011 ppm) for repeated oral doses.

Because estimated plateau brain concentrations may more closely reflect concentrations at the target tissue, Bayer proposed extrapolating results from the rat mixed-dose study to the biomonitoring study using an adjustment factor. Because 70 divided by 4 equals 17.5, or is approximately 20, Bayer proposed multiplying results in the biomonitoring study by this adjustment factor.

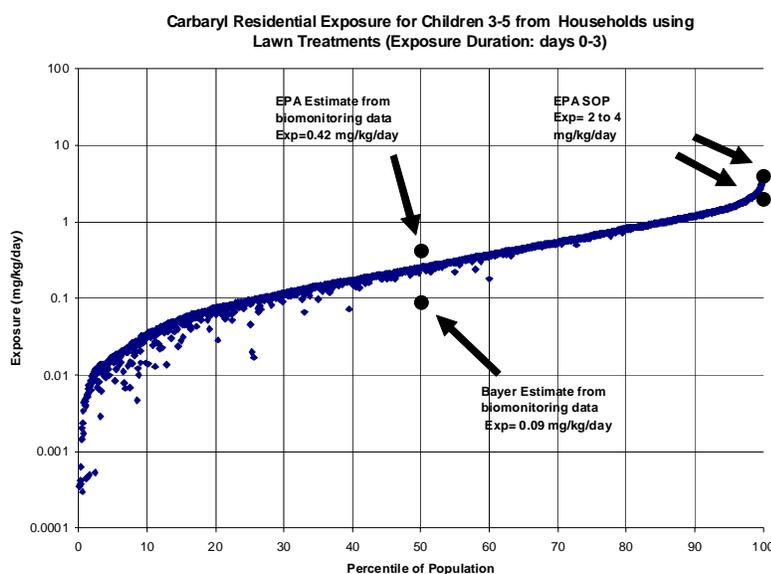
### 3. Summary

Bayer has proposed, that because of carbaryl's pharmacokinetic and pharmacodynamic characteristics, peak or plateau concentrations of carbaryl in brain are a more accurate indicator of risk than is total absorbed dose. These characteristics include rapid oral absorption, prolonged dermal absorption, brief inhibition of acetylcholinesterase, and short half-life in the body.

The Agency has completed three exposure assessments for carbaryl. One assessment is a deterministic assessment based upon the *Standard Operating Procedures For Residential Exposure Assessment*. The other two exposure assessments included a probabilistic model, CARES (Cumulative And Aggregate Risk Evaluation System), which calculated distributions of exposures, and the biological monitoring study described above in Section 3.1. All three assessments gave similar results (See Figure 3). The Agency has based its current regulatory position upon the results of the deterministic assessment and has used the biological monitoring data and the probabilistic assessment results to characterize exposure and risks associated with carbaryl lawn use.

The three exposure assessments described above all gave similar results, but only evaluated total exposure and did not consider peak exposure in the target tissue. At issue in this SAP meeting is whether an estimate of peak exposure in target tissue is appropriate to assess carbaryl exposure and if these results can modify results from traditional exposure assessments.

**Figure 3. Results of Agency Exposure Assessments**



## Supporting Tables & Figures

Following are tables and figures from the Bayer metabolism study and the Bayer mixed-dose study.

**Table 1. Average Total Radioactive Residue (ppm).** Intravenous dose = 0.80 mg/kg/day

Time (hr)	Whole Blood	Plasma	RBC	Brain
0.083 = 5min	1.2536	2.1310	1.0551	0.7360
0.167 = 10 min	1.1079	1.8310	0.9059	0.4137
0.333 = 20 min	0.9025	1.6940	0.6676	0.2299
0.5	0.7890	1.4345	0.4935	0.1431
1	0.5016	0.8508	0.2959	0.0562
2	0.3253	0.5798	0.1509	0.0251
4	0.1253	0.2080	0.0974	0.0130
8	0.064	0.1061	0.0488	0.0094

**Table 2. Average Total Radioactive Residue (ppm).** Oral dose = 1.08 mg/kg

Time (hr)	Whole Blood	Plasma	RBC	Brain
0.25 = 15 min	0.9004	1.4414	0.4427	0.1253
0.5 = 30 min	0.7270	1.1922	0.3191	0.0613
1	0.5741	0.810	0.1828	0.0339
2	0.4079	0.5406	0.1016	0.0282
4	0.2875	0.4046	0.1146	0.0202
6	0.1517	0.1921	0.0659	0.0145
12	0.0471	0.0559	0.0220	0.0052
24	0.0180	0.0140	0.0073	0.0030

**Table 3. Average Total Radioactive Residue (ppm). Dermal dose = 17.25 mg/kg**

Time (hr)	Whole Blood	Plasma	RBC	Brain
0.25 = 15 min	0.0092	0.0090	0.0006	0.0051
0.5 = 30 min	0.0181	0.0287	0.0059	0.0068
1	0.0104	0.0119	0.0018	0.0020
2	0.0490	0.0968	0.0263	0.0089
4	0.0690	0.1467	0.0441	0.0111
6	0.0484	0.1020	0.0203	0.0052
12	0.0252	0.0441	0.0072	0.0046
24	0.0178	0.0239	0.0070	0.0034

Tables 1-3 above, were adapted from Tables 6, 2, and 4 respectively of Bayer metabolism study.

**Table 4. Half-life of Total Radioactive Residue**

Tissue (Route)	10 mg/kg	1 mg/kg	0.084 mg/kg
Plasma (Oral)	1.5	1.2	
Plasma (IV)	1.8 (0.40) <sup>a</sup>	1.2	
Plasma (Mixed) <sup>b</sup>			0.50
RBC (Oral)	1.2	0.75	
RBC (IV)	1.0	0.6	
RBC (Mixed) <sup>b</sup>			0.80
Brain (Oral)	0.8 (0.30) <sup>a</sup>	0.35	
Brain (IV)	0.6 (0.45) <sup>a</sup>	0.25	
Brain (Mixed) <sup>b</sup>			0.33

<sup>a</sup>Half-life of actual carbaryl residues in the alpha phase

<sup>b</sup>In "mixed-dose study", samples taken following the second oral dose from a study where rats received two oral doses of 0.084 mg/kg, one hour apart (at time 0 and 1 hr), and a dermal dose of 0.871 mg/kg at time 0, which remained on the rats skin for 2 hours.

**NOTE:** Bayer reported that:

"It was not possible to estimate half-life for carbaryl itself in the alpha phase following oral dosing at 1 and 10 mg/kg because it dissipated so rapidly, and levels beyond the peak could not be reliably quantified using the standard flow cell radiometric detector. However, at 0.084 mg/kg oral dose a different detection method was employed (fraction collector), and it was possible to estimate half life."

**Adapted from Table 3, page 12 of Bayer proposal.**

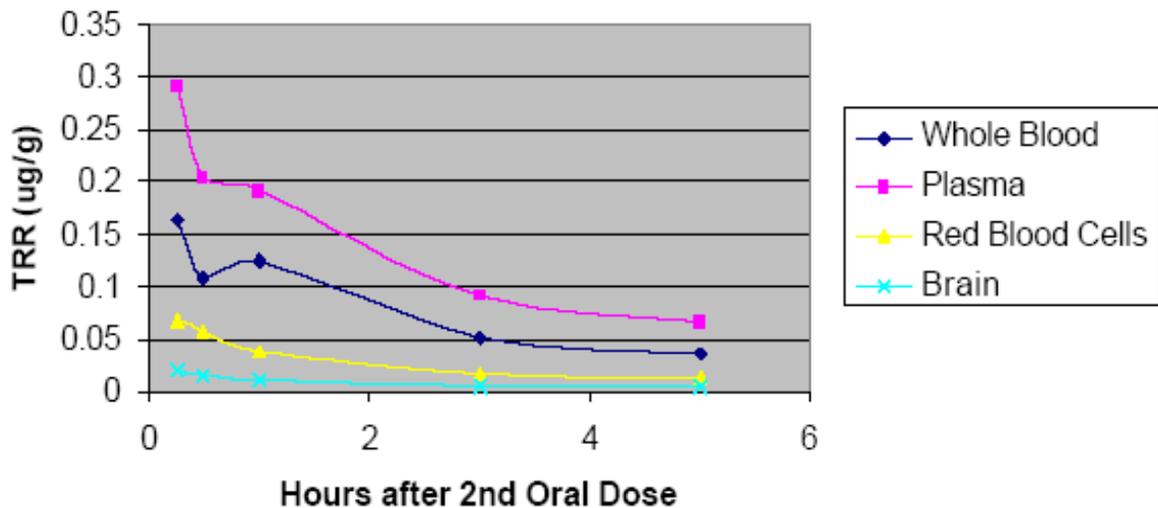
**Table 5. Average Total Radioactive Residue (ppm) From Mixed Dose Study<sup>a</sup>.**  
 Concurrent oral and dermal dosing. Samples taken after 2nd oral dose

Time (hr)	Whole Blood	Plasma	RBC	Brain
0.25	0.1633	0.2905	0.0664	0.0206
0.5	0.1075	0.2031	0.0570	0.0129
1	0.1237	0.1899	0.0382	0.0099
3	0.0511	0.0904	0.0161	0.0034
5	0.0359	0.0648	0.0127	0.0043

<sup>a</sup> In "mixed-dose study", samples taken following the second oral dose from a study where rats received two oral doses of 0.084 mg/kg, one hour apart (at time 0 and 1 hr), and a dermal dose of 0.871 mg/kg at time 0, which remained on the rats skin for 2 hours.

From Table 1, p 26 of mixed-dose study

**Figure 4. Average Total Radioactive Residue (ppm) From Mixed Dose Study<sup>a</sup>**



<sup>a</sup>In "mixed-dose study", samples taken following the second oral dose from a study where rats received two oral doses of 0.084 mg/kg, one hour apart (at time 0 and 1 hr), and a dermal dose of 0.871 mg/kg at time 0, which remained on the rats skin for 2 hours.

From Figure 7, p 26 of mixed-dose study

**Table 6. Total Radioactive Residue (TRR) and Metabolites Identified in Brain after Mixed-Dose Study**

Time	TRR (ppm)	1-Naphthol Sulfate		1-Naphthol		Carbaryl	
		% TRR	TRR (ppm)	% TRR	TRR (ppm)	% TRR	TRR (ppm)
15 min	0.0206	12	0.0025	12	0.0025	22	0.0045
30 min	0.0129	18	0.0023	6	0.00077	18	0.0023
1 h	0.0099	23	0.0023	5	0.00050	15	0.0015
3 h	0.0034	28	0.00095	4	0.00014	13	0.00044
5 h	0.0043	19	0.00082	6	0.00026	15	0.00064

Adapted from Table 2, p 17 of mixed-dose study

## Appendices

### Appendix 1

E-file name: **Bayer proposal.pdf**

*Application of carbaryl pharmacokinetic data in the estimation of potential post-application health risks associated with broadcast lawn care products.* Ross, J; Driver, J; Lunchik, C. Bayer CropScience. September 8, 2004. 40 pages.

### Appendix 2

E-file name: **Bayer metabolism study.pdf**

*Metabolism of [<sup>14</sup>C] Carbaryl in Rats.* Krolski, et al. Bayer CropScience. May 7, 2004. 230 pages.

### Appendix 3

E-file name: **Bayer mixed-dose study.pdf**

*Metabolism and Pharmacokinetics of [<sup>14</sup>C] Carbaryl in Rats Following Mixed Oral and Dermal Exposure.* Krolski, et al. Bayer CropScience. May 7, 2004. 53 pages.

### Appendix 4

E-file name: **MOE\_Derivation\_HtM\_EPAScenario\_10Jun04.xls**

Spreadsheet for calculation of plateau brain concentrations, Bayer CropScience.

### Appendix 5

E-file name: **Proposed Path in Rats.pdf**

Proposed Path in Rats