UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

August 2, 2006

MEMORANDUM

Subject: Methomyl and Oxamyl: Review of two randomized double blind ascending oral dose studies; Human, non-guideline

Methomyl: MRID 44721401, PC Code: 090301, D308718
Oxamyl: MRID 44912301, PC Code: 103801, D308714

TXR No.: 0052872

From: Elissa Reaves, Ph.D., Toxicologist
Reregistration Branch II
Health Effects Division (7509C)

Elissa Reaves 8/2/06

Through: Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
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To: Kelly Sherman, Chemical Review Manager
Reregistration Branch 1
Special Review and Reregistration Division (7508C)

Action Requested:
Review the two double blind ascending oral dose studies with oxamyl and methomyl in human male subjects (MRID 44912301, 44721401, respectively). Both of these human studies were presented to the Human Studies Review Board (HSRB) in April 2006. The HSRB concluded that both human studies were ethically and scientifically reliable for use in risk assessment.

Conclusions:

1. Oxamyl:

Under the conditions of this ascending oral dose study in humans, 0.09 mg/kg/day represents a level where 7-12% plasma and RBC ChE inhibition was observed. Three of 5

volunteers at this dose (0.09 mg/kg/day) exhibited greater than 20% plasma ChE inhibition. Therefore, 0.06 mg/kg/day is considered the NOAEL.

This study is classified as **Acceptable/Non-guideline**. Additionally, the Agency generated BMD and BMDL estimates based on the RBC ChE data from this study. The resulting RBC BMD_{10} is 0.083 mg/kg with $BMDL_{10}$ of 0.069 mg/kg. Please refer to the *N*-methyl carbamate (NMC) cumulative risk assessment for details.

2. Methomyl:

Under the conditions of this ascending oral study, the NOAEL for methomyl in humans is < 0.1 mg/kg. The LOAEL is 0.1 mg/kg, based on decreased peak RBC cholinesterase activity (-19%).

This study is classified as **Acceptable/non-guideline.** The Agency generated BMD and BMDL estimates based on the RBC ChE data from this study. The resulting BMD_{10} is 0.040 mg/kg with $BMDL_{10}$ of 0.028 mg/kg. Please refer to the *N*-methyl carbamate (NMC) cumulative risk assessment for details.

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DATA EVALUATION RECORD

OXAMYL/103801
NON-GUIDELINE STUDY

STUDY TYPE: ASCENDING ORAL TOXICITY STUDY IN HUMANS
MRID 44912301

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 74-2005

Robert H. Ross

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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

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EPA Secondary Reviewer: Anna Lowit, Ph.D. **Signature:**
Reregistration Branch 2, Health Effects Division (7509C) **Date** 8/2/06

Template version 11/01

TXR#: 0052872

DATA EVALUATION RECORD

STUDY TYPE: Ascending Oral Toxicity - Humans, non-guideline.

PC CODE: 103801 **DP BARCODE:** 308714

TEST MATERIAL (PURITY): Ethanimidothioic acid, 2-(dimethylamino)-N{[(methlamino)carbonyl]oxy}]-2-oxo, methyl ester (97.6%)

SYNONYMS: Oxamyl technical, DPX-D1410 Technical, Methyl 2-(dimethylamino)-N-[(methylamino)carbonyl)oxy)-2-oxo-ethanimidothioate, Methyl N',N'-dimethyl-N-[(methyl carbonyl)oxythiooxaminidate

CITATION: McFarlane, P., Freestone, S. (1999) A randomized double blind ascending oral dose study with oxamyl. Inveresk Clinical Research, Riccarton, Edinburgh, EH14 4AP, Scotland. Laboratory Project ID: HLO-1998-01505, August 10, 1999. MRID 44912301. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company, Newark, Delaware 19714-0050

EXECUTIVE SUMMARY: In a non-guideline, ascending acute oral toxicity study (MRID 44912301), 40 healthy human male volunteers, aged 19 - 39 years, were each given a single oral dose of oxamyl technical (approximately 97.6% a.i., batch #: DPX-D140-196) in a gelatin capsule at doses of 0, 0.005, 0.015, 0.03, 0.06, 0.09, or 0.15 a.i. mg/kg bw. Volunteers were admitted to the clinic the afternoon prior to the morning dosing. The volunteers were fasted for 9 hours prior to breakfast. Study volunteers were dosed approximately 5 minutes following a "standard" breakfast, and observed for two nights and one follow-up visit 7 (± 2) days post-dose. All volunteers remained under close medical and nursing supervision throughout the study. The study was conducted as a double-blind ascending-dose escalation clinical trial, and each male was treated at one of nine dosing sessions. Volunteers received a complete screening physical examination, testing for Hepatitis B, C, and HIV infection, and drug-screening of urine within 14 days of study commencement. Blood pressure and heart rate were measured at screening (within 14 days prior to dosing), 16 hours pre-dose (admission), 30 minutes pre-dose, and 1, 2, 3, 4, 8 ,and 24 hours post-dose. Oral temperature was recorded at screening, 16 hours and 30 minutes pre-dose, and 2, 4, and 24 hours post-dose. A 12-lead ECG was obtained at screening, 30 minutes pre-dose, and 30 minutes, 1, 2, and 24 hours post-dose. Hematology and clinical chemistry testing was performed at screening, 30 minutes pre-dose, and 24 hours post-dose. Urinalysis was conducted at screening and 24 hours post-dose. Pupillometry was performed 16 hours and 30 minutes pre-dose, and 1, 2, 3, 4, 8, and 24 hours post-dose. Saliva was collected and quantified by weight 16 hours and 30 minutes pre-dose, and 1, 2, 3, 4, 8, and 24 hours post-dose. Plasma and red blood cell cholinesterase activity were assayed at screening, and 2 days, 16

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hours, and 30- minutes pre-dose, and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, and 24 hours post-dose, and at 7 (± 2) days post-dose.

Clinical signs were reported by a total of 7 individuals from both the placebo (3 volunteers) and oxamyl dose groups (4 volunteers). These clinical observations did not correspond with peak ChE inhibition and were therefore not considered to be treatment related. Clinical observations from the placebo volunteers included bleeding gums, headache, fever, tremor, muscular pains, and right sided groin pain. Symptoms reported by the two volunteers in the 0.015 mg/kg dose group included headache (pre-dose), brief nausea (57 minutes post-dose to 61 minutes), and abdominal pain (46 hours post-dose to 46.5 hours post-dose). Examination of the volunteer with the brief nausea revealed no inhibition of cholinesterase activity or effects on pupil size or salivation and so was deemed unlikely related to the test compound. An earache was noted by one volunteer (46 hours post-dose to 46.5 hours post-dose) of the 0.03 mg/kg dose group. At 0.15 mg/kg, one volunteer experienced a headache (6 hours 50 minutes lasting 15 hours 15 minutes) and increased generalized sweating (10 hours 50 minutes lasting 3 hours 55 minutes). Both of these symptoms were considered possibly related to study compound but further investigation revealed the time course of symptoms were not consistent with the cholinesterase activity inhibition observed. Therefore, the adverse events were not likely to be truly related to the test compound.

The mean percent change in plasma cholinesterase activity was statistically decreased compared to placebo in the high dose (0.15 mg/kg) beginning at the first time point (-14%, 15 min) until 3 hours post-dosing (-8%), with peak inhibition at 45 minutes post-dosing (43%, $p<0.001$). Plasma cholinesterase activity returned to baseline by 6 hours post-dosing. For the group exposed to 0.09 mg/kg, plasma cholinesterase activity was significantly inhibited starting at 75 minutes post-dosing (-12% peak, $p=0.026$) until 2 hours post-dosing (-10%, $p=0.039$) with recovery at 3 hours post-dosing. Within the 0.06 mg/kg dose group, the maximum plasma cholinesterase inhibition was -7% at 75 minutes post-dosing (non-statistical, $p=0.22$). Plasma cholinesterase activity was similar to placebo in the 0.005, 0.015 and 0.03 mg/kg dose groups at all time points. However, when the linear trend was tested for dose at each time point, the test was significant for every time point except at 4, 8, 12, and 24 hours, and 7 days post-dosing. The inclusion or exclusion of outlying values did not alter the results for plasma cholinesterase activity.

The mean RBC cholinesterase activity of the high dose group (0.15 mg/kg) was inhibited significantly beginning at 30 minutes (-23%, $p<0.001$) with peak inhibition at 45 and 60 minutes (-28% and -27%, respectively with $p<0.001$ for both) until 2 hours post-dosing (-8%, $p=0.011$) and recovery to baseline by 3 hours post-dosing. For the 0.09 mg/kg dose group, the mean RBC cholinesterase activity was significantly decreased only at 30 minutes (-7%, $p=0.016$) with recovery following at 45 minutes post-dosing. RBC cholinesterase activity was statistically similar to placebo at all time points in the 0.005, 0.015, 0.03, and 0.06 mg/kg dose groups. Analysis of a linear trend for RBC cholinesterase activity by dose at varying time points indicated significance from 30 minutes until 105 minutes post-dosing.

Saliva weight when examined with outliers was increased in the two highest dose groups at 1 hour post-dosing compared to the placebo group. A linear trend was observed for saliva weight (change from baseline), which increased with increasing dose and was only significant ($p=0.002$)

at the 1 hour time point. The significance of saliva weight and dose was not achieved at any other time point during the study.

There were no significant decreases in minimum pupil size and recovery pupil size relative to baseline between any dose level and placebo, at any of the time points. Significant increases in recovery pupil size were observed at 2,4, 8 and 24 hour post-dosing in the 0.005 mg/kg group when compared to placebo. However, increases in pupil size are contrary to the expected response to cholinergic stimulation by the test substance.

Under the conditions of this ascending oral dose study in humans, 0.09 mg/kg/day represents a level where 7-12% plasma and RBC ChE inhibition was observed. Three of 5 volunteers at this dose (0.09 mg/kg/day) exhibited greater than 20% plasma ChE inhibition. Therefore, 0.06 mg/kg/day is considered the NOAEL.

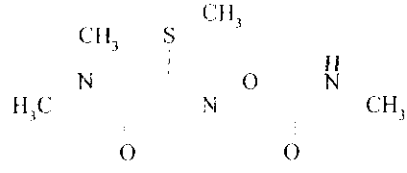
This study is classified as **Acceptable/Non-guideline**. Additionally, the Agency generated BMD and BMDL estimates based on the RBC ChE data from this study. The resulting RBC BMD_{10} is 0.083 mg/kg with $BMDL_{10}$ of 0.069 mg/kg. Please refer to the *N*-methyl carbamate (NMC) cumulative risk assessment for details. The oxamyl human study was reviewed by the Human Studies Review Board (HSRB) in April 2006. The HSRB concluded the human study was ethically and scientifically reliable for use in risk assessment.

COMPLIANCE: Signed and dated Good Clinical Practice Compliance, Quality Assurance, and No Data Confidentiality statements were provided. The study was conducted in accordance with the Declaration of Helsinki, 1964, as amended by the 29th Medical World Assembly in Tokyo (1975), the 35th Medical World Assembly in Venice, 1983, 41st Medical World Assembly in Hong Kong, 1989, and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Oxamyl technical

Description:	White solid; "appeared to be stable" under study conditions. Analyses were conducted to assess the accuracy, homogeneity and stability of the preparation prior to the initiation of dosing
Lot/Batch #:	Batch No. DPX-D1410-196
Purity:	Approx. 97.6% a.i., approx. 2.25% inerts. .
CAS # of TGAI:	23135-22-0
Chemical structure:	

2. Vehicle and/or positive control: Oxamyl technical was administered in a gelatin capsule as an oxamyl/lactose blend. Placebo was lactose administered in a matching capsule.

3. **Volunteers:**

Species:	Human (Male)	
Strain:	N.A.	
Age/weight at dosing:	Age: 19 - 39 years; Weight: 60.8 - 95.5 kg	
Source:	Volunteers recruited and screened for inclusion in the study by Inveresk Clinical Research clinical staff.	
Housing:	Admitted to clinic the afternoon prior to morning dosing, and discharged approx. 24 hours post-dose.	
Diet:	"Standard" breakfast approx. 5 minutes before dosing; fasted until approx. 3 hours post-dose and then allowed decaffeinated fluids; and a light lunch approx. 4 hours post dosing.	
Water:	Water consumption not specified.	
Environmental conditions:	**Temperature:**	Not specified
	Humidity:	Not specified
	Air changes:	Not specified
	Photoperiod:	Not specified
Acclimation period:	Volunteers admitted to clinic the afternoon before dosing the next a.m.	

B. STUDY DESIGN and METHODS:

1. **Study dates:** Start: September 28, 1998, End: not given

2. **Volunteer population:** Forty volunteers were assigned to the test groups noted in Table 1, and were admitted to the clinic the afternoon before the study. All volunteers were healthy white males; thirty-four were non-smokers and six were previous smokers. Four volunteers were non-drinkers, and 36 reported the regular consumption of approximately 1 to 20 "units" of alcohol/week (1 unit = 1 glass wine or beer, or measure of spirit).

3. **Blinding:** The study design was double blind and placebo controlled, with the exception of Session 1 in which both volunteers received placebo. Dose escalation was not to occur if there were clinically significant symptoms/signs of carbamate toxicity or if any volunteer had ≥40% inhibition of RBC cholinesterase at a single time point or ≥ 25% inhibition at 2 consecutive time points. If there were associated symptoms/signs of carbamate toxicity, no further administration of that particular dose would occur. The allocation of the test substance or placebo was randomized and based on the randomization code generated by the Statistics Department of Inveresk Research. A copy of the randomization code was held by the ICR phamacist where it was required for dispensing purposes and by the Regulatory Affairs Department at Inveresk Research. Sealed disclosure envelopes were also provided to ICR. In the event of an emergency requiring identification of the drug administered to a volunteer, the Study Director could request that the envelope be opened.

4. **Experimental Design:** Approximately 5 minutes after the completion of a "standard" breakfast, the volunteers were given a single dose of an oxamyl/lactose blend (Batch No. DPX-D140-196) or placebo in a gelatin capsule while sitting, with 150 mL water. The dosing schedule is presented in Table 1. Based on available animal data, the starting dose (0.005 mg/kg bw) was predicted to have no detectable effects on humans. The volunteers remained seated or recumbent until approximately 3 hours post-dosing, when they were allowed to be ambulant and have decaffeinated fluids. A light lunch was provided approximately 4 hours post-dosing. Volunteers were discharged about 24 hours post-dosing, with their agreement to return within 7 (±) days for follow-up evaluation of well-

being, any outstanding adverse events, and for measurement of plasma and red blood cell (RBC) cholinesterase activity.

TABLE 1. Study design

Doses Administered (mg/kg bw) and number of volunteers

Session Numbers	0 (Placebo)	0.005	0.015	0.03	0.06	0.09	0.15
1	2						
2	1	1					
3	1	4	1				
4	1		4	1			
5	1			4	1		
6	1				4	1	
7	1					4	
8	1						1
9	1						4
Total Volunteers	10	5	5	5	5	5	5

Data obtained from p. 20, MRID 44912301.

5. **Clinical evaluation:** Volunteers received a complete screening physical examination, testing for Hepatitis B, C, and HIV infection, and drug-screening of urine within 14 days of study commencement. Blood pressure and heart rate were measured at screening (within 14 days prior to dosing), 16 hours pre-dose (admission), 30 minutes pre-dose, and 1, 2, 3, 4, 8 ,and 24 hours post-dose. Oral temperature was recorded at screening, 16 hours and 30 minutes pre-dose, and 2, 4, and 24 hours post-dose. A 12-lead ECG was obtained at screening, 30 minutes pre-dose, and 30 minutes post-dose, and 1, 2, and 24 hours post-dose. Hematology and clinical chemistry testing was performed at screening, 30 minutes pre-dose, and 24 hours post-dose. Urinalysis was conducted at screening and 24 hours post-dose. Pupillometry was performed 16 hours and 30 minutes pre-dose, and 1, 2, 3, 4, 8, and 24 hours post-dose using the optical unit (pupilscan, hand-held electronic pupillometer). Saliva was collected and quantified by weight 16 hours and 30 minutes pre-dose, and 1, 2, 3, 4, 8, and 24 hours post-dose by having the volunteers place 2 sterilin-treated, weighed dental rolls opposite the 2nd molar on the upper cheek pouch on both sides for 5 minutes. The dental rolls were then replaced in the sterilin and the pre- and post-collection weights were used to determine the salivary weight. Plasma and red blood cell cholinesterase activity were assayed at screening, and 2 days, 16 hours, and 30-minutes pre-dose, and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, and 24 hours post-dose, and at 7 (± 2) days post-dose. Plasma and red cell fraction (except screening and post-study samples) were separated and immediately snap frozen in liquid nitrogen. The collected plasma and red cell samples were assayed for cholinesterase activity according to the method of Ellman (1961) adapted as a clinical chemistry kit and analyzed on a Hitachi clinical chemistry analyzer (IR/SOP/CLC/043).

6. **Statistics:** The SAS (v6.07) statistical package was used to perform statistical analyses. The parameters evaluated included the mean, standard deviation, minimum, maximum, and number at each timepoint for pupillometry (initial, minimum, recovery, and change from initial to minimum), vital signs, saliva collection, and plasma and RBC cholinesterase activity. These parameters were analyzed and summarized by dose level and timepoint. The percentage change from baseline at each time point was calculated on an individual basis and tabulated by dose level. Baseline was defined as the mean of all available pre-dose values (for that individual) (screening, 2 days, 16 hours, or 30 minutes pre-dose).

A repeated measures analysis of variance (ANOVA) - including terms for dose level, timepoint, and dose level by timepoint interaction - were used to analyze the percentage change from baseline in RBC and plasma cholinesterase activity, pupillometry, and saliva collection. At each timepoint, a test for linear trend with dose was performed using a linear contrast. Using the error variance from the ANOVA, pairwise comparisons between placebo and each dose level were carried out at each timepoint using the Student's 't'-test. If the test for linear trend was significant at the 5% level, then the pairwise comparisons at that timepoint were not adjusted for multiple comparisons. If the test for linear trend was not significant at the 5% level, a Bonferroni adjustment was applied to the pairwise comparisons at that timepoint (i.e., each comparison was tested at the 0.83% significance level). Treatment group LSMeans (i.e., means adjusted for any imbalance in the model) were presented together with the significance level of the 't' tests and the test for linear trend.

Normality of distribution was examined using a Shapiro-Wilk test, while homogeneity of variance was assessed by plotting the residuals against the predicted values for the model. If there was significant non-normality that could not be resolved by transforming the data, the data were analyzed excluding outliers. If the omission of outliers had no effect on the conclusions, the results of the full data set only were reported.

Descriptive statistical methods were used to summarize demographic data, ECG, urinalysis, and adverse events by dose level and, where appropriate, by timepoint. Adverse events were summarized under each dose level by tabulating the frequency of reports of each unique event, and were coded using the WHO Adverse Reaction Terminology (1997).

II. RESULTS:

A. CLINICAL FINDINGS:

1. **Clinical observations:** A total of 13 clinical effects were reported by a total of 7 study volunteers. No clinical signs were reported for the 0.005, 0.06 or 0.09 mg/kg dose groups. Three placebo volunteers reported clinical signs that included bleeding gums; secondary to trauma, headache, fever, tremor "feeling shaky", muscular pains, and discomfort in right groin; and slightly enlarged inguinal nodes on the right side were noted. In the 0.015 mg/kg group, clinical signs were reported for 3 volunteers and

included nausea (4 minutes) and headache; pre-dose, and abdominal pain; 46 hours post-dose for 30 minutes. An earache was reported by one volunteer in the 0.03 mg/kg group. Headache, sweating and epistaxis (nosebleed) were reported in the 0.15 mg/kg dose group by one volunteer. The sweating began 10 hours 50 minutes post-dose and lasted for 3 hours and 55 minutes. The nose bleed began 22 hours and 50 minutes post-dose. All reported clinical signs in all volunteers were gone by the post-study visit. The symptoms reported by the volunteers typically do not correspond with the peak ChE inhibition and fall outside the time of ChE recovery. Therefore, the clinical observations are not considered to be treatment related.

2. **Vital signs and ECG**: No dose group had changes in vital signs or ECGs.

3. **Cholinesterase inhibition:** see Tables 2 and 3.

Individual cholinesterase: Four of the 5 volunteers of the high dose (0.15 mg/kg) group demonstrated a greater than -40% inhibition of plasma cholinesterase activity from that individuals baseline (baseline consisted of the mean of screening, -2 days, -16 hours, and -30 minutes pre-dosing). One of these 4 volunteers also has greater than -40% RBC ChE inhibition. The first volunteer had -46%, -45%, and -42% plasma cholinesterase activity at 60, 75, and 90 minutes post-dosing. The corresponding peak RBC ChE inhibition occurred at 60 minutes (-43%). The second volunteer also displayed inhibited plasma cholinesterase activity at 30 (-54%), 45 (-58%), 60 (-49%), and 75 (-39%) minutes post-dosing. Peak RBC ChE inhibition of -38% occurred at 45 minutes post-dosing. Plasma cholinesterase inhibition occurred beginning at 30 minutes (-61%) in the third volunteer until 60 minutes (-40%) post-dosing. A maximum of -34% RBC ChE inhibition occurred at 45 minutes post-dosing. Plasma cholinesterase inhibition for the fourth volunteer occurred at 45 minutes post-dosing only (-41%) with peak RBC ChE inhibition of -35% at 45 minutes post-dosing.

Three of the 5 volunteers of the 0.09 mg/kg dose group exhibited a -20% or greater inhibition of plasma cholinesterase activity beginning at 45 minutes post-dosing. These 3 volunteers of the 0.09 mg/kg dose group exhibited -23% plasma (-7% RBC at 45 minutes), -21% plasma (-18% RBC at 30 minutes), and -20% plasma (-15% RBC at 120 minutes) cholinesterase inhibition at 45, 75, and 120 minutes post-dosing, respectively.

Plasma cholinesterase: Statistical analysis of the group mean by time point was not performed. Instead, statistical analysis was performed on the percent change from baseline (average of values at screening, -2 days, -16 hr, and -30 min). The mean percent change in plasma cholinesterase activity was statistically decreased compared to placebo in the high dose (0.15 mg/kg) beginning at the first time point (-14%, 15 min) until 3 hours post-dosing (-8%), with peak inhibition at 45 minutes post-dosing (43%, $p<0.001$). Plasma cholinesterase activity returned to baseline by 6 hours post-dosing. For the group exposed to 0.09 mg/kg, plasma cholinesterase activity was significantly inhibited starting at 75 minutes post-dosing (-12% peak, $p=0.026$) until 2 hours post-dosing (-10%, $p=0.039$) with recovery at 3 hours post-dosing. Maximum plasma ChE inhibition varied among volunteers with a maximum of -23% at 45 minutes until approximately 2 hours

(-20%) post-dosing. Within the 0.06 mg/kg dose group, the maximum plasma cholinesterase inhibition was -7% at 75 minutes post-dosing (non-statistical, p=0.22). Plasma cholinesterase activity was similar to placebo in the 0.005, 0.015 and 0.03 mg/kg dose groups at all time points. However, when the linear trend was tested for dose at each time point, the test was significant for every time point except at 4, 8, 12, and 24 hours, and 7 days post-dosing. The inclusion or exclusion of outlying values did not alter the results for plasma cholinesterase activity.

Red blood cell (RBC) cholinesterase: As with plasma cholinesterase activity, RBC cholinesterase activity was analyzed as the percent change from baseline compared to placebo at varying time points post-dosing. The mean RBC cholinesterase activity of the high dose group (0.15 mg/kg) was inhibited significantly beginning at 30 minutes (-23%, $p<0.001$) with peak inhibition at 45 and 60 minutes (-28% and -27%, respectively with $p<0.001$ for both) until 2 hours post-dosing (-8%, p=0.011) and recovery to baseline by 3 hours post-dosing. For the 0.09 mg/kg dose group, the mean RBC cholinesterase activity was significantly decreased only at 30 minutes (-7%, p=0.016) with recovery following at 45 minutes post-dosing. Volunteer variation of RBC ChE activity at this dose at 30 minutes ranged from +8% to -18%. RBC cholinesterase activity was statistically similar to placebo at all time points in the 0.005, 0.015, 0.03, and 0.06 mg/kg dose groups. Analysis of a linear trend for RBC cholinesterase activity by dose at varying time points indicated significance from 30 minutes until 105 minutes post-dosing.

Table 2. Plasma and RBC cholinesterase activity change from baseline (%) over time in volunteers receiving oxamyl (outlying values included)

Time	Dosage Group (mg/kg bw)						
	0	0.005	0.015	0.03	0.06	0.09	0.15
Plasma cholinesterase (mean ±SD)							
15 mins postdose	-1.3 ±6.3	-3.0 ±7.7	2.7 ±11.5	0.4 ±2.1	-2.4 ±1.7	-4.1 ±8.6	-14.1*±12.0
30 mins postdose	-4.7 ±4.8	-4.8 ±6.2	0.1 ±8.0	2.0 ±1.6	-5.4 ±3.5	-5.6 ±9.1	-35.9**±21.9
45 mins postdose	-7.3 ±7.4	-4.6 ±5.3	0.1 ±8.7	0.5 ±2.3	-2.1 ±14.7	1.2 ±17.7	-43.4**±14.7
1 h postdose	-1.7 ±5.7	1.3 ±7.0	0.7 ±7.4	-1.2 ±4.8	-5.6 ±4.8	-6.2 ±8.4	-40.4**±7.2
1 h 15 mins postdose	-1.5 ±5.4	-0.4 ±6.9	3.6 ±8.2	-0.3 ±3.3	-7.1 ±4.8	-11.6* ±8.2	-35.9**±6.0
1 h 30 mins postdose	-3.3 ±4.7	-2.6 ±6.4	3.4 ±8.1	-2.2 ±5.9	-4.1 ±4.9	-10.1 ±6.4	-30.2**±7.5
1 h 45 mins postdose	-4.0 ±5.1	-1.3 ±6.7	3.0 ±10.3	-0.8 ±4.5	-3.9 ±4.2	-9.5 ±4.5	-25.3**±4.6
2 h postdose	-1.0 ±4.4	1.9 ±5.7	2.8 ±7.3	-2.1 ±2.1	-5.7 ±3.3	-10.2* ±6.0	-20.9**±4.8
3 h postdose	0.4 ±5.7	3.2 ±5.1	6.6 ±5.3	5.4 ±2.3	-3.3 ±5.4	1.3 ±5.9	-8.0 ±5.8
4 h postdose	-1.0 ±5.3	0.9 ±4.1	7.4 ±7.3	3.5 ±4.8	-1.0 ±4.5	1.4 ±3.5	-1.7 ±2.7
6 h postdose	-4.4 ±5.0	-11.7 ±7.0	3.9 ±15.5	0.9 ±4.9	-4.5 ±3.3	-1.7 ±4.6	5.8 ±26.0
8 h postdose	-3.7 ±5.3	-8.5 ±5.1	10.8 ±16.4	2.0 ±4.5	-2.4 ±4.9	0.8 ±4.8	2.5 ±24.8
12 h postdose	-5.5 ±6.7	-13.0 ±3.7	2.6 ±16.2	1.8 ±7.3	-4.0 ±2.3	-2.2 ±5.1	1.6 ±16.8
RBC cholinesterase (mean ±SD)							
15 mins postdose	4.9 ±10.6	2.0 ±7.6	-0.4 ±10.8	4.8 ±14.6	-1.3 ±7.2	1.0 ±8.9	-2.3 ±16.6
30 mins postdose	7.8 ±11.2	11.6 ±4.8	1.5 ±8.5	5.5 ±10.9	-2.4 ±7.8	-7.3*±8.3	-23.2**±13.8
45 mins postdose	6.5 ±10.8	-0.2 ±6.2	-4.8 ±16.0	3.0 ±13.8	-4.3 ±8.2	0.2 ±12.2	-27.9**±12.7
1 h postdose	9.4 ±10.3	4.9 ±8.1	3.0 ±3.9	1.9 ±16.3	5.9 ±11.1	-0.3 ±7.5	-27.1**±10.1
1 h 15 mins postdose	5.5 ±10.3	2.5 ±12.4	1.0 ±9.9	7.3 ±11.3	1.6 ±14.0	-0.7 ±7.2	-16.8**±15.0
1 h 30 mins postdose	11.1 ±8.8	3.2 ±9.9	2.9 ±6.6	6.0 ±11.1	4.5 ±9.0	1.8 ±6.2	-15.9**±9.3
1 h 45 mins postdose	4.5 ±14.7	2.1 ±11.0	2.5 ±9.5	-0.1 ±10.5	1.9 ±4.1	-1.1 ±5.8	-9.2*±7.2
2 h postdose	7.9 ±9.7	0.3 ±2.8	-2.3 ±7.3	-0.5 ±5.4	-2.8 ±12.6	-2.1 ±7.8	-8.0 ±9.7
3 h postdose	10.3 ±10.9	9.2 ±9.5	-3.7 ±9.5	7.8 ±13.4	3.2 ±11.6	-0.2 ±14.0	-0.4 ±6.8
4 h postdose	12.4 ±10.4	8.4 ±11.5	9.6 ±8.2	-0.5 ±5.2	2.3 ±7.2	3.0 ±13.4	3.7 ±11.0
6 h postdose	3.5 ±13.8	10.6±10.7	4.8 ±12.9	6.5 ±7.5	5.1 ±5.2	21.3*±14.0	10.9 ±6.6

Data obtained from pp. 415-416, and 419-420, MRID 44912301.
*Statistically significant at $p < 0.05$, compared with controls.
** *Statistically significant at* $p \leq 0.001$, *compared with controls.*
mins = minutes, h = hours

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Table 3. Mean values for Plasma and RBC cholinesterase activity in all volunteers receiving oxamyl (outlying values included)

Time	Dosage Group (mg/kg bw)						
	0	0.005	0.015	0.03	0.06	0.09	0.15
Plasma cholinesterase							
screening	5013±648.9	5306±817	5082±1008	5314±842	5125±804	5014±552	4682±837
Day -2	5685±671.5	6541±929	5221±784	6153±1409	6137±1000	5301±586	5158±935
-16 h	5473±603.9	6379±1017	5460±1030	5664±1412	5787±900	5142±412	4945±920
-30 mins	5346±593.6	6117±1259	5388±844	5943±964	5809±951	5297±791	4871±777
15 mins postdose	5321±767.4	5902±934	5455±1367	5776±1055	5571±812	4978±605	4158*±465
30 mins postdose	5130±639.4	5799±954	5320±1175	5881±1151	5396±830	4894±496	3140**±1153
45 mins postdose	4981±646.0	5825±1050	5308±1135	5785±1091	5527±758	5233±878	2758**±739
1 h postdose	5287±651.3	6180±1088	5355±1192	5677±1047	5385±833	4859±448	2913**±566
1 h 15 mins postdose	5307±703.7	6051±894	5484±1082	5737±1059	5303±843	4574*±285	3138**±567
1 h 30 mins postdose	5208±682.6	5919±914	5475±1057	5609±981	5466±818	4658±386	3431**±743
1 h 45 mins postdose	5174±676.5	6014±1025	5450±1105	5708±1082	5480±838	4692±301	3673**±705
2 h postdose	5325±579.8	5988±1105	5440±1040	5650±1114	5380±796	4667*±533	3890**±758
3 h postdose	5402±640.4	6282±971	5628±916	6057±1053	5518±919	5268±602	4513±793
4 h postdose	5337±725.4	6151±1023	5680±1063	5951±1096	5663±974	5268±446	4822±787
6 h postdose	5149±665.0	5340±580	5462±1060	5793±1016	5462±939	5110±521	5105±1122
8 h postdose	5189±688.0	5555±759	5809±1018	5878±1190	5591±1079	5242±535	4941±979
12 h postdose	5080±634.9	5278±663	5361±889	5867±1227	5500±966	5082±503	4938±812
24 h postdose	5301±744.9	5738±840	5713±840	6276±1111	5996±1010	5355±457	4568±484
post study	5672±640.8	5978±1000	5450±767	6038±1179	5838±722	5292±542	5180±975
RBC cholinesterase							
screening	8433±1539	8898±943	9808±1242	9457±1007	9006±633	7870±901	8557±585
Day -2	12063±928	12380±1105	12143±1114	11866±601	12194±1179	11349±1344	11863±1065
-16 h	11501±1200	12839±1419	12127±1023	11776±991	12570±784	11092±587	11299±850
-30 mins	11457±868	12534±1148	11714±655	12599±619	12246±699	11437±2026	10686±1644
15 mins postdose	11402±1430	11887±890	11397±1346	11959±1547	11324±501	10512±1238	10346±1822
30 mins postdose	11698±1336	13009±862	11645±1442	12061±1458	11198±602	9618*±713	8125**±1477
45 mins postdose	11551±1303	11656±1157	10887±1861	11766±1654	11015±1144	10407±1249	7605**±1043
1 h postdose	11878±1358	12250±1379	11781±596	11642±1898	12178±1286	10354±767	7695**±874

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1 h 15 mins *postdose*	11458±1328	11914±1197	11606±1785	12298±1816	11655±1372	10309±655	8753**±1079
1 h 30 mins *postdose*	12088±1448	12028±1261	11760±571	12095±1230	12015±1027	10612±1244	8881**±640
1 h 45 mins *postdose*	11286±1239	11911±1469	11748±1426	11418±1314	11719±663	10270±649	9599*±444
2 h postdose	11703±1121	11931±981	11170±865	11380±941	11191±1699	10174±909	9713*±731
3 h postdose	11946±1130	12758±1481	11056±1580	12309±1493	11901±1685	10321±967	10530±217
4 h *postdose*	12211±1394	12628±1309	12573±1528	11363±747	11757±904	10649±869	10956±873
6 h postdose	11187±1231	12910±1618	11986±1565	12164±906	12102±984	12536±436	11723±320
8 h postdose	11850±1876	11047±974	12679±1865	12826±1170	11050±1159	11947±1502	11570±773
12 h postdose	12056±1323	12628±1687	11337±1063	11641±1152	11764±753	12066±1145	12056±997
24 h postdose	11639±1418	11710±1218	12906±1605	12131±1406	12275±471	11574±1002	11809±1638
post study	12333±1887	13120±865	13368±1274	12984±1386	12775±1379	12296±1463	12690±1534

Data obtained from pp. 419-420, and 435-447, MRID 44912301.
*Statistically significant at $p < 0.05$, compared with controls.
** Statistically significant at $p \leq 0.001$, compared with controls.
mins = minutes, h = hours

4. **Pupillometry**:

With Outliers: When all outlying values were included, the percent change of the mean initial pupil size from baseline (-30 minutes pre-dose) compared to placebo was decreased in the 0.06 and 0.09 mg/kg dose groups one hour post-dose (-14.6%, p=0.4 and -17.7% , p=0.77, respectively). The 0.06 mg/kg group mean initial pupil size returned to +2.6% of baseline by 4 hours post-dose, and the 0.09 mg/kg group returned to +1.9% of baseline at 8 hours post-dose. The high-dose group mean pupil size (initial) was reduced the most at 3 hours post-dose (-10.7% of baseline, p=0.42); subsequent values did not show a gradual increase over time. None of these reductions were statistically significant.

Without Outliers: When the outlying values were included however, the test for distributional assumption of normality (Shapiro-Wilk test) was not satisfied. As a result, the pupillometry data were re-analyzed without outliers. Approximately 75% of the outliers were found in the 0.005 mg/kg dose level. When the outlying values were excluded, a linear trend (Bonferroni adjustment) was apparent at every time point.

There were no significant decreases in minimum pupil size and recovery pupil size relative to baseline between any dose level and placebo, at any of the time points. Significant increases in recovery pupil size were observed at 2,4, 8 and 24 hour post-dosing in the 0.005 mg/kg group when compared to placebo.

5. **Increased salivation:** Saliva weight (including outliers) was increased in the 0.09 and 0.15 mg/kg groups (97.6%, p=0.19; and 160.7%, p= 0.01, change from baseline at -30 minutes) at 1 hour post-dose when compared to the placebo group. A linear trend with

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increasing dose was only significant (p=0.002) at the 1 hour time point; percentage change from baseline saliva collection increased with dose. At subsequent time points during the study, neither the mean saliva weight nor the trend with dose were significant.

B. CLINICAL CHEMISTRY:

1. **Hematology, clinical chemistry, and urinalysis:** No treatment-related effects were found at any test dose.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

The study authors concluded that the 0.005, 0.015, 0.03, and 0.06 mg/kg dose groups had no treatment-related and biologically relevant inhibition in RBC or plasma cholinesterase activity, increase in salivary secretion, decrease in pupil size, or effect on ECGs, vital signs, body temperature, clinical chemistry, urinalysis, or clinical signs.

"The 0.9 mg/kg dose group did not have any statistically significant increases in salivary secretion. There were no compound-related effect on ECGs, vital signs, body temperature, hematology, clinical chemistry, urinalysis, or clinical signs at any timepoint. Plasma cholinesterase activity was decreased at the 1 hour 15 minute (-11.6% from baseline), 1 hour 30 minutes (-10.1% from baseline), and 2 hours (-10.2 from baseline). timepoint, and RBC cholinesterase activity was statistically decreased at 30 minutes (-7.3%). Although these depressions were statistically significant, they were not considered to be adverse since they were relatively small in magnitude (less than 20%) and similar to depressions in plasma and RBC cholinesterase that occurred in individual volunteers within the placebo group during the course of the study. A statistically significant decrease in initial pupil size occurred at the 1 hour timepoint. This was not of clinical significance as minimum and recovery pupil sizes for that timepoint were not significantly decreased and there were no adverse effects on blood cholinesterase."

"The 0.15 mg/kg dose group had no compound related effects on ECG, vital signs, body temperature, hematology, clinical chemistry, urinalysis or clinical signs at any timepoint. At the 1-hour assessment, there was a statistically significant decrease in initial pupil size and a statistically significant increase in saliva collected. In addition, statistically significant depressions in plasma cholinesterase activity were present at all time points up to and including 3 hours post-dosing and statistically significant depressions in RBC cholinesterase activity was observed from 30 minutes up to and including 1 hour 45 minutes. The period of maximum depression occurred at 45 and 60 minutes for plasma cholinesterase and from 30 to 60 minutes for RBC cholinesterase. Plasma and RBC cholinesterase activities returned to baseline within 4 and 3 hours following administration of the test substance, respectively."

B. EPA CONCLUSIONS:

No dose group had changes in respiratory rate, ECGs, vital signs, hematology, clinical chemistry, urinalysis, or clinical signs. There were no significant decreases in minimum and recovery pupil sizes in any dose group compared to placebo. Plasma and RBC cholinesterase activity typically returned to normal by 3 hours post-dosing in all groups. In the high dose (0.15 mg/kg) plasma and RBC cholinesterase activity both peaked (43% and 28%, respectively) at 45 minutes post-dosing with recovery by 3 to 4 hours post-dosing. Plasma cholinesterase inhibition peaked at 75 minutes (-12%) and recovered by 3 hours post-dosing in the 0.09 mg/kg dose group. RBC cholinesterase inhibition was statistically decreased (-7%) at 30 minutes only. No differences in plasma or RBC cholinesterase activities were observed in the other dose groups compared to control. Under the conditions of this ascending oral dose study in humans, 0.09 mg/kg/day represents a level where 7-12% plasma and RBC ChE inhibition was observed. Three of 5 volunteers at this dose (0.09 mg/kg/day) exhibited greater than 20% plasma ChE inhibition. Therefore, 0.06 mg/kg/day is considered the NOAEL.

Additionally, the Agency used the RBC ChE inhibition time-course data for input into the Agency's BMDS model. The BMD_{10} is 0.083 mg/kg and $BMDL_{10}$ of 0.069 mg/kg. The BMD and BMDL were considered for the NMC carbamate cumulative risk assessment for refinement of the interspecies extrapolation factor for oxamyl.

C. DEFICIENCIES:

There were no study deficiencies identified that would have affected the outcome and conclusions of this study.

DATA EVALUATION RECORD

METHOMYL/90301
NON-GUIDELINE STUDY

STUDY TYPE: ASCENDING ACUTE ORAL TOXICITY STUDY IN HUMANS
MRID 44721401

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Life Sciences Division
Oak Ridge National Laboratory
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Task Order No. 74-2005

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Disclaimer

This review may have been altered subsequent to the contractors' signatures above.

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EPA Reviewer: Elissa Reaves, Ph.D. **Signature:**
Reregistration Branch 2, Health Effects Division (7509C) **Date:** 8/2/06
EPA Secondary Reviewer: Anna Lowit, Ph.D. **Signature:**
Reregistration Branch 2, Health Effects Division (7509C) **Date:** 8/2/06

TXR#: 0052872

DATA EVALUATION RECORD

STUDY TYPE: Ascending Acute Oral Toxicity - Humans, non-guideline.

PC CODE: 090301 **DP BARCODE:** 308718

TEST MATERIAL (PURITY): Ethanimidothioic acid, N-[{(methylamino)carbonyl}oxy]-, methyl ester (Methomyl) (89%)

SYNONYMS: Lannate® SP, S-methyl N-[(methylcarbamoyl)oxy]thioacetimidate, Lannate 90, DPX-X1179.

CITATION: McFarlane, P., Sanderson, J.B., Freestone, S. (1998) A randomized double blind ascending oral dose study with methomyl to establish a no adverse effect level. *Inveresk Clinical Research, Riccarton, Edinburgh, EH14 4AP, Scotland.* Laboratory Project ID: HLO-1998-00969, November 30, 1998. MRID 44721401. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company, Newark, Delaware 19714-0050

EXECUTIVE SUMMARY: In a non-guideline, ascending acute oral toxicity study (MRID 44721401), 19 healthy human male volunteers, ages 18 - 40 years, were each given a single oral dose of a methomyl formulation (Lannate® SP, approximately 89% a.i., batch #: T 101397-00) in a capsule at doses of 0, 0.1, 0.2, or 0.3 a.i. mg/kg bw following a "standard" breakfast, and observed for two nights and one follow-up visit 7 (± 2) days post-dose. Volunteers were admitted to the clinic the afternoon prior to the morning dosing and were requested to fast for 9 hours prior to breakfast. The study was conducted as a double-blinded ascending-dose escalation clinical trial, and each male was treated at one of four dosing sessions. All volunteers remained under close medical and nursing supervision throughout the study. Parameters evaluated were physical examination and urinalysis at screening and 24 hours post-dosing; vital signs (i.e., blood pressure and heart rate), salivary quantity by weight (secreted within 5 minutes), and pupillometry at 16 hours pre-dosing, 30 minutes pre-dosing, and 1, 2, 3, 4, 8, and 24 hours post-dosing; oral temperature at screening, 16 hours pre-dosing, 30 minutes pre-dosing, 2, 4, and 24 hours post-dosing; 12-lead electrocardiogram (ECG) obtained at screening, 30 minutes pre-dosing, 30 minutes post-dosing, and 1, 2, and 24 hours post-dosing; continuous ECG monitoring from 30 minutes pre-dosing through 3 hours post-dosing; hematology and clinical chemistry at screening, 30 minutes pre-dosing, and 24 hours post-dosing; and blood for plasma and red blood cell (RBC) cholinesterase activities at screening, 16 hours pre-dosing (at admission), 30 minutes

pre-dosing, every 15 minutes for the first 2 hours post-dosing, and then at 2, 3, 4, 6, 8, 12, and 24 hours post-dosing, and finally 7 days post-dosing.

Four volunteers (one volunteer at each concentration) throughout the 4 Sessions demonstrated a greater than 40% inhibition of RBC cholinesterase activity from that individuals baseline [Session 1: 0.1 mg/kg, -43.5% at only 8 hrs post-dose (likely spurious); Session 2: 0.3 mg/kg, -47% at 45 minutes post-dosing and headache at 105 minutes post-dosing (headache lasted approximately 1 hour); Session 3: 0.3 mg/kg, -43% at 45 minutes post-dosing; Session 4: 0.2 mg/kg, -41% at 75 minutes post-dosing]. RBC cholinesterase activity returned to baseline by 6 hours post-dosing in all volunteers with the exception of the spurious event in the one volunteer receiving 0.1 mg/kg (8 hrs post-dosing).

A dose-response relationship was observed in all dose groups for plasma and RBC cholinesterase activity. In addition, cholinesterase activity for both plasma and RBC was consistent for timing of peak effect and time to recovery. In the high dose group, the mean percent change in RBC cholinesterase activity was statistically significantly decreased compared to placebo activity from the first time point at 15 minutes (-18.6%) to 4 hours post-dosing (-5.0%), with peak inhibition at 45 minutes (-35.2%) and recovery at 6 hours post-dosing. At the mid-dose, mean percent change in RBC cholinesterase activity was statistically significantly decreased compared to placebo activity beginning at 45 minutes post-dosing (-20.0%) until 2 hours post-dosing (-16.2%), with peak inhibition at 1 hour and 30 minutes (-27.9%) and recovery at 3 hours post-dosing. The mean percent change in RBC cholinesterase activity for the low dose (0.1 mg/kg) was statistically similar to placebo activity at all time points. However, at 60, 75, and 90 minutes post-dosing, the percent change in mean RBC cholinesterase activity was -14.6% , -19.0%, and -10.5% of the mean group baseline level, respectively. The timing of the mean RBC cholinesterase activity coincides with the inhibition of RBC cholinesterase activity in the mid- and high-dose groups.

The mean percent change in plasma cholinesterase activity was statistically significantly decreased compared to placebo activity in the high dose (0.3 mg/kg) beginning at 15 minutes post-dosing (-9.8%) until 4 hours post-dosing (-8.1%), with peak inhibition at 45 minutes (-21.1%) and recovery at 6 hours post-dosing. In the mid-dose group (0.2 mg/kg) the mean percent change from baseline plasma cholinesterase activity compared to placebo was statistically significantly decreased beginning at 45 minutes post-dosing (-11.5%) until 2 hours post-dosing (-10.3%) with peak inhibition at 1 hour 45 minutes (-13.5%) and recovery at 3 hours post-dosing. Mean percent change in plasma cholinesterase activity for the low dose (0.1 mg/kg) was statistically similar to placebo activity at all time points. Plasma cholinesterase activity was only statistically significantly decreased at 2 hours post-dosing (-7.2%) when outliers were excluded.

Increases in saliva weight were dose-related at the one-hour time point, with the 0.3 mg/kg volunteers at 60.3% of baseline weight, suggesting a potentially cholinergic response to the treatment.

Three volunteers had increased total bilirubin at least once during the study. The first volunteer (0.1 mg/kg) had increased total bilirubin at 30 minutes pre-dosing only. The

second (0.2 mg/kg) and third (0.3 mg/kg) volunteer had increased total bilirubin at screening, 30 minutes pre-dosing, and 24 hours post-dosing.

No dose group had changes in pupillary size, respiratory rate, ECGs, vital signs, hematology, clinical chemistry, urinalysis, or clinical signs of cholinergic effects (with the exception of the 0.3 mg/kg individual who complained of a transient headache, and the early increase in salivation).

Under the conditions of this ascending oral study, the NOAEL for methomyl in humans is < 0.1 mg/kg. The LOAEL is 0.1 mg/kg, based on decreased peak RBC cholinesterase activity (-19%).

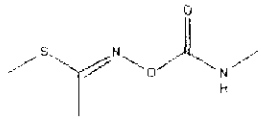
This study is classified as **Acceptable/non-guideline.** The Agency generated BMD and BMDL estimates based on the RBC ChE data from this study. The resulting BMD_{10} is 0.040 mg/kg with $BMDL_{10}$ of 0.028 mg/kg. Please refer to the *N*-methyl carbamate (NMC) cumulative risk assessment for details. The methomyl human study was reviewed by the Human Studies Review Board (HSRB) in April 2006. The Board concluded the human study was ethically and scientifically reliable for use in risk assessment.

COMPLIANCE: Signed and dated Good Clinical Practice Compliance, Quality Assurance, and No Data Confidentiality statements were provided. The study was conducted in accordance with the Declaration of Helsinki, 1964, as amended by the 29th Medical World Assembly in Venice, 1983, 41st Medical World Assembly in Hong Kong, 1989, and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** Lannate® SP
   Description: White solid; "appeared to be stable" under study conditions
   Lot/Batch #: Batch No. T101397-00
   Purity: Approx. 89% a.i., approx. 11% inerts
   CAS # of TGAI: 16752-77-5



2. **Vehicle and/or positive control:** Methomyl formulation was administered in a gelatin capsule. Placebo was hydrated silica (Batch No. H-10-7) administered in a matching capsule.

3. **Volunteers:**

Species:	Human (Male)	
Strain:	N.A.	
Age/weight at dosing:	Age: 18 - 40 years; Weight: 60.6 - 91.9 kg	
Source:	Volunteers recruited and screened for inclusion in the study by ICR clinical staff.	
Housing:	Admitted to clinic the afternoon prior to morning dosing, and discharged approx. 24 hours post-dose.	
Diet:	"Standard" breakfast approx. 5 minutes before dosing; fasted until approx. 3 hours post-dose and then allowed decaffeinated fluids; and a light lunch approx. 4 hours post dosing.	
Water:	Water consumption not specified.	
Environmental conditions:	**Temperature:**	Not specified
	Humidity:	Not specified
	Air changes:	Not specified
	Photoperiod:	Not specified
Acclimation period:	Volunteers admitted to clinic the afternoon before dosing the next a.m.	

B. STUDY DESIGN and METHODS:

1. **Study dates:** Start: November 12, 1997 End: November 30, 1998

2. **Volunteer population:** Volunteers (19 total) were assigned to the test groups noted in Table 1, and were admitted to the clinic the afternoon before the study. With the exception of one Asian, all volunteers were white males. All were healthy; 14 were non-smokers, and 5 were previous smokers. Two volunteers were non-drinkers, and the remaining reported they regularly consumed moderate amounts of alcohol.

3. **Blinding:** The study design was double blind and placebo controlled. Dose escalation was not to occur if there were clinically significant symptoms/signs of carbamate toxicity or if any volunteer had ≥40% inhibition of RBC cholinesterase without associated symptoms/signs of carbamate toxicity. If there were associated symptoms/signs of carbamate toxicity, no further administration of that particular dose would occur. The allocation to active or placebo was randomized and a copy of the randomization code was held by the ICR pharmacist where it was required for dispensing purposes and by the Regulatory Affairs Department at Inveresk Research. Sealed disclosure envelopes were also provided to ICR. In the event of an emergency requiring identification of the test material administered to a volunteer, the study director could request that the envelope by opened. The blindness of the study was broken on completion of group three in order to assess the link between the cholinesterase inhibition and active test compound. A new randomized code was generated for a modified Session 4 dosed with 0.2 mg/kg bw or placebo.

4. **Experimental Design:** Approximately 5 minutes after the completion of a "standard" breakfast, the volunteers were given a single dose of the formulated product Lannate®SP (Batch No. T101397-00) at dosing levels of 0, 0.1, 0.2, or 0.3 a.i. mg/kg bw while sitting, with 150 mL water. The formulation contained approximately 89% methomyl as the a.i., and 11% inerts. Control volunteers were given a placebo (hydrated silica - Batch No. H-10-7) by capsule. The doses were adjusted for a test substance with approximately 89% purity.

   During the first of 4 sessions, one volunteer received a placebo and the other received the 0.1 mg/kg body weight dose. The second session consisted of one volunteer receiving a placebo, 4 receiving the 0.1 mg/kg dose, and one volunteer receiving the 0.3 mg/kg dose. Session 3 consisted of 1 volunteer receiving the placebo and 4 receiving 0.3 mg/kg dose with the 1 volunteer at 0.5 mg/kg being dropped. A greater than 40% RBC cholinesterase inhibition occurred in Session 3 and therefore, upon unblinding the study, Session 4 was modified to include 1 volunteer receiving placebo and 4 receiving 0.2 mg/kg instead of 0.5 mg/kg methomyl. The study was then reblinded. All volunteers were observed "under close medical and nursing supervision" for approximately 24 hours after substance administration. Volunteers were weighed on an unspecified date. Volunteers were released, with their agreement to return within 7 (± 2) days for follow-up observation of continued well-being, evaluation of any outstanding adverse events, and for measurement of plasma and red blood cell (RBC) cholinesterase activity.

TABLE 1. Study design

Doses of methomyl administered (mg/kg bw) and number of volunteers

Session Numbers	0 (Placebo)	0.1	0.2	0.3	0.5
1	1	1			
2	1	4		1	
3	1			4	1 (dropped)*
4	1		5		
Total Volunteers = 19	4	5	5	5	0

Data obtained from p. 34, MRID 44721401.
* No dosing at 0.5 mg/kg occurred in Session 3 as >40% RBC inhibition was obtained.

5. **Clinical evaluation:** Systolic and diastolic blood pressure and heart rate were measured at screening, admission (16 hours pre-dose) and 30 minutes pre-dose, and at 0.5, 1, 2, 3, 4, 8, 16, and 24 hours post-dose. A 12-lead electrocardiogram (ECG) was obtained at screening (within 14 days prior to study commencement), 30 minutes pre-dose, 30 minutes post-dose, and 1, 2, and 24 hours post-dose. Blood was collected at screening, 30 minutes pre-dose, and at 0.25, 0.5, 0.75, 1.0, 1.25,

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1.5, 1.75, 2, 3, 4, 6, 8, 12, and at 24 hours and 7 (± 2) days post-dose. Plasma and red cell fractions were immediately separated and chilled in liquid nitrogen, and assayed for cholinesterase activity using the method of Ellman, 1961 (as adapted as a clinical chemistry kit and analyzed on a Hitachi Clinical Chemistry Analyzer). Urinalysis was evaluated at screening and 24 hours post-dose while hematology and clinical chemistry at screening, 30 minutes pre-dosing, and 24 hours post-dosing. Body temperature was obtained at screening, 16 hours pre-dosing, 30 minutes pre-dosing, 2, 4, and 24 hours post-dosing.

Pupillometry was conducted at 16 hours pre-dose, 30 minutes pre-dose, and 1, 2, 3, 4, 8, and 24 hours post-dose, using the optical unit (pupilscan, hand-held electronic pupillometer). Saliva was collected and quantified by weight at 16 hours pre-dose, 30 minutes pre-dose, and 1, 2, 3, 4, 8, and 24 hours post-dose by having the volunteers place 2 sterilin-treated, weighed dental rolls opposite the 2nd molar both on the upper cheek pouch on both sides for 5 minutes. The dental rolls were then replaced in the sterilin and the pre- and post-collection weights were used to determine the salivary weight. Single-channel, continuous ECG monitoring was performed from 30 minutes pre-dose to 3 hours post-dose.

6. **Statistics:** The SAS (v6.07) statistical package was used to perform statistical analyses. The mean, standard deviation, minimum, maximum, and number of volunteers for pupillometry (initial, minimum, recovery, and change from initial to minimum), vital signs, saliva collection, and plasma and RBC cholinesterase activity was analyzed and summarized by dose level and time point. When both 16 hour pre-dose and 30 minute pre-dose values were taken, baseline (for each individual) was defined as the mean of these 2 values.

   A repeated measures analysis of variance (ANOVA) - including terms for dose level, time point, and dose level by time point interaction - were used to analyze the percentage change from baseline for RBC and plasma cholinesterase activity, pupillometry, and saliva collection. At each time point, a test for linear trend with dose was performed using a linear contrast. Using the error variance from the ANOVA, pairwise comparisons between placebo and each dose level were carried out at each time point using the Student's 't'-test. If the test for linear trend was significant at the 5% level, then the pairwise comparisons at that time point were not adjusted for multiple comparisons. If the test for linear trend was not significant at the 5% level, a Bonferroni adjustment was applied to the pairwise comparisons at that time point (i.e., each comparison was tested at the 1.7% significance level). Treatment group LSMeans (i.e., means adjusted for any imbalance in the model) were presented together with the significance level of the 't' tests and the test for linear trend.

   Normality of distribution was examined using a Shapiro-Wilk test, while homogeneity of variance was assessed by plotting the residuals against the predicted values for the model. If there was significant non-normality that could not be resolved by transforming the data, the data was analyzed excluding outliers. If the omission of outliers had no effect on the conclusions, the results of the full data set only were reported.

Descriptive statistical methods were used to summarize demographic details, electrocardiogram, urinalysis, and adverse events by dose level and, where appropriate, by time point. Adverse events were summarized under each dose level by tabulating the frequency of reports of each unique event, and by tabulating the number of volunteers experiencing one or more events (as classified by the WHO Adverse Reaction Terminology).

II. RESULTS:

A. CLINICAL OBSERVATIONS:

1. **Individual cholinesterase inhibition:** Four volunteers throughout the 4 Sessions demonstrated a greater than -40% inhibition of RBC cholinesterase activity from that individuals baseline (baseline consisted of the mean of 16 hours pre-dosing and 30 minutes pre-dosing; or when one value was missing, consisted of the single pre-dose value). In Session 1, one volunteer receiving 0.1 mg/kg had approximately -43.5% RBC cholinesterase inhibition (from self baseline) only 8 hours post-dosing. This was likely a spurious event since RBC ChE activity had returned to baseline for the previous time points. In Session 2, one volunteer receiving 0.3 mg/kg had approximately -47% RBC cholinesterase inhibition (from self baseline) at 45 minutes post-dosing. This individual also reported a single occurrence of a headache (that did not require treatment) 105 minutes after dosing but ended within one hour. In Session 3, at 45 minutes post-dose, one volunteer receiving 0.3 mg/kg dose had approximately -43.0% RBC cholinesterase inhibition. At this point in the study, the Study Director and the Sponsor agreed a minimum effect level had been reached. The study was then unblinded and the data reviewed. Since the minimum effect level had been reached (criterion of -40% or greater RBC cholinesterase inhibition), the highest dose (0.5 mg/kg) in Session 3 was dropped. Subsequently, Amendment 1 to the protocol was issued detailing that Session 4 would consist of 6 volunteers, one receiving placebo and five receiving 0.2 mg/kg of the test compound. The study was then re-blinded. In Session 4, one volunteer exhibited a -41% decrease in RBC cholinesterase activity at 75 minutes post-dosing. As a result of the RBC inhibition in Session 4, the Sponsor decided that no further dose groups were required.

   With the exception of the spurious decreased RBC cholinesterase activity in the 0.1 mg/kg volunteer (at 8 hours post-dosing), the other 3 study volunteers had normal RBC cholinesterase activity by 6 hours post-dosing (Table 2).

2. **Group cholinesterase inhibition:** The group mean ± standard deviation of plasma and RBC cholinesterase activity of all volunteers is provided in Table 3. Statistical analysis of the group mean by time point was not performed. Instead, statistical analysis was performed on the percent change of cholinesterase activity of the baseline (individual) compared to placebo. This was exhibited by the difference of the mean cholinesterase activity at specific post-dosing time points with the mean baseline cholinesterase activity. Baseline is defined as the mean of the two pre-dose values (16h and 30 min pre-dose) for each individual of the dose group. If one of the pre-dose values was missing for an individual, baseline was taken as the non-missing assessment. The mean percent change from baseline plasma and RBC cholinesterase activity for each dose group is presented in Table 2. In addition,

statistical analysis including and excluding outliers was performed for plasma cholinesterase activity only and is also presented in Table 2.

For plasma cholinesterase activity, the statistical significance was similar regardless of whether outliers where included or excluded from the analysis. The mean percent change in plasma cholinesterase activity (including outliers) was statistically significantly decreased compared to placebo activity in the high dose (0.3 mg/kg) beginning at 15 minutes post-dosing (-9.8%) until 4 hours post-dosing (-8.1%), with peak inhibition at 45 minutes (-21.1%, $p<0.001$) and recovery at 6 hours post-dosing. In the mid-dose group (0.2 mg/kg) the mean percent change from mean baseline plasma cholinesterase activity (including outliers) compared to placebo was statistically significantly decreased beginning at 45 minutes post-dosing (-11.5%) until 2 hours post-dosing (-10.3%) with peak inhibition at 1 hour 45 minutes (-13.5%, $p<0.001$) and recovery at 3 hours post-dosing. Mean percent change in plasma cholinesterase activity for the low dose (0.1 mg/kg) was statistically similar to placebo activity at all time points when outliers were included. When outliers were excluded, the mean percent change in plasma cholinesterase activity for the low dose (0.1 mg/kg) at 2 hours post-dosing was statistically significant from placebo activity (-7.2%).

The mean percent change in RBC cholinesterase activity (including outliers) was statistically significantly decreased compared to placebo from the first time point at 15 minutes (-18.6%, $p<0.05$) to 4 hours post-dosing (-5.0%, $p<0.05$), with peak inhibition at 45 minutes (-35.2%, $p<0.001$) and recovery at 6 hours post-dosing in the high-dose group (0.3 mg/kg). At the mid-dose, mean percent change in RBC cholinesterase activity (including outliers) was statistically significantly decreased compared to placebo activity beginning at 45 minutes post-dosing (-20.0%, $p<0.05$) until 2 hours post-dosing (-16.2%, $p<0.05$), with peak inhibition at 1 hour and 30 minutes (-27.9, $p<0.001$) and recovery at 3 hours post-dosing. The mean percent change in RBC cholinesterase activity for the low dose (0.1 mg/kg) was statistically similar to placebo at all time points. However, at 60, 75, and 90 minutes post-dose, the mean percent change in RBC cholinesterase activity was -14.6% , -19.0%, and -10.5% below the group mean baseline level, respectively. This decrease in mean RBC cholinesterase activity coincides with the inhibition of RBC cholinesterase activity in the mid- and high-dose groups. The statistical analysis for RBC cholinesterase activity was for all volunteers, the RBC analysis without outliers was not presented.

TABLE 2. Plasma and RBC cholinesterase activity change from baseline (mean ± SD%) over time (with* and without* outliers) in volunteers receiving methomyl

Time	Dosage group (mg/kg bw)			
	0	0.1	0.2	0.3
Plasma cholinesterase				
15 mins post-dose	-1.31 ± 5.0	-3.07 ± 3.6	-2.46 ± 2.8	-9.76*± 2.*
30 mins post-dose	-2.87 ± 4.8	-6.64 ± 3.9	-7.87 ± 3.7	-15.85**± 2.2**
45 mins post-dose	-1.4 ± 3.8	-5.63 ± 2.1	-11.48*± 5.5**	-21.08**± 4.9**
1 h post-dose	-0.31 ± 3.0	-4.52 ± 3.4	-11.03*± 4.2**	-16.59**± 2.2**
1 h 15 mins post-dose	-0.79 ± 4.7	-2.95 ± 5.7	-13.32**± 5.1**	-19.67**± 2.9**
1 h 30 mins post-dose	-2.42 ± 5.7	-5.91 ± 3.9	-12.90*± 2.5**	-14.84**± 4.2**
1 h 45 mins post-dose	-2.67 ± 4.8	-5.57 ± 1.8	-13.52*± 2.0**	-15.89**± 3.8**
2 h post-dose	-0.99 ± 3.8	-7.22 ±3.6*	-10.34*± 3.3*	-14.12**± 5.6**
3 h post-dose	-1.29 ± 4.8	-1.07 ± 4.7	-5.04 ± 4.6	-10.87*± 3.0**
4 h post-dose	0.02 ± 7.3	-2.51 ± 2.1	-1.26 ± 3.2	-8.11*± 3.8*
6 h post-dose	0.56 ± 6.4	-0.18 ± 3.8	2.06 ± 5.0	0.24 ± 3.1
RBC cholinesterase				
15 mins post-dose	5.83 ± 9.8	3.15 ± 17.5	-1.19 ± 9.3	-18.57*± 12.4
30 mins post-dose	-1.78 ± 5.6	-9.2 ± 13.0	-12.42 ± 5.6	-31.96**± 3.6
45 mins post-dose	-2.93 ± 14.9	-2.45 ± 12.1	-19.98*± 14.1	-35.25**± 10.4
1 h post-dose	-3.98 ± 17.3	-14.61 ± 11.6	-24.71*± 9.4	-27.28*± 7.5
1 h 15 mins post-dose	-4.26 ± 5.8	-19.04 ± 9.3	-27.59*± 10.7	-26.79*± 7.3
1 h 30 mins post-dose	-0.3 ± 5.6	-10.5 ± 10.6	-27.87**± 7.4	-23.20*± 7.4
1 h 45 mins post-dose	1.82 ± 5.9	-3.57 ± 11.5	-22.19*± 4.9	-22.41*± 10.7
2 h post-dose	5.84 ± 14.0	-8.91 ± 11.2	-16.20*± 5.6	-16.02*± 8.7
3 h post-dose	12.06 ± 12.7	-2.13 ± 12.5	-1.34 ± 7.4	-12.90*± 16.5
4 h post-dose	11.35 ± 10.1	4.97 ± 12.3	-2.28 ± 8.8	-5.05*± 8.5
6 h post-dose	6.22 ± 12.8	-5.89 ± 16.3	14.75 ± 6.4	-1.99 ± 6.7

Data obtained from pp. 432-433, and 436-437, MRID 44721401.
With Outliers: *Statistically significant at $p < 0.05$, compared with controls.
** Statistically significant at $p \leq 0.001$, compared with controls.
Without Outliers: *Statistically significant at $p < 0.05$, compared with controls.
**Statistically significant at $p \leq 0.001$, compared with controls.
mins = minutes, h = hours
Baseline is defined as the mean of the two pre-dose values (16h and 30 min pre-dose) for each individual of the dose group. If one of the pre-dose values was missing for an individual, baseline was taken as the non-missing assessment. The mean baseline value for the group was used to determine the % change from baseline

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TABLE 3. Mean Plasma and RBC cholinesterase activity (mean ± standard deviation) over time in all volunteers receiving methomyl

Time	Dosage group (mg/kg bw)			
	0	0.1	0.2	0.3
Plasma cholinesterase				
16 h pre-dose	5532.5 ±744	5265.8 ±942.5	5535.4 ±844.1	5658.6 ±574.0
30 mins pre-dose	5588.8 ±663.4	5273.6 ±938.6	5272.8 ±591.9	5664.8 ±533.7
15 mins post-dose	5480.5 ±644.4	5085.6 ±755.5	5264.2 ±631.5	5115.8 ±574.2
30 mins post-dose	5402.0 ±715.8	4913.2 ±859.0	4971.6 ±613.3	4763.8 ±458.4
45 mins post-dose	5487.0 ±737.0	4981.0 ±943.9	4777.0 ±606.7	4458.6 ±388.4
1 h post-dose	5537.0 ±622.4	5044.4 ±994.6	4789.2 ±470.0	4714.6 ±353.6
1 h 15 mins post-dose	5515.8 ±699.8	5119.2 ±965.2	4660.6 ±420.3	4555.6 ±536.6
1 h 30 mins post-dose	5427.3 ±728.8	4952.2 ±857.2	4697.4 ±533.3	4837.6 ±675.1
1 h 45 mins post-dose	5420.0 ±770.4	4967.8 ±831.7	4671.4 ±605.4	4774.0 ±642.5
2 h post-dose	5504.8 ±685.0	4887.0 ±888.2	4833.6 ±549.2	4879.8 ±718.0
3 h post-dose	5505.5 ±868.7	5218.2 ±973.7	5115.4 ±561.0	5054.6 ±612.8
4 h post-dose	5580.0 ±927.9	5145.2 ±976.8	5326.6 ±622.3	5218.6 ±717.2
6 h post-dose	5584.5 ±691.3	5250.6 ±872.4	5286.2 ±682.1	5683.0 ±647.8
8 h post-dose	5580.0 ±797.6	5224.0 ±788.2	5430.6 ±685.3	5611.0 ±544.8
12 h post-dose	5377.5 ±675.5	5210.4 ±828.0	5366.6 ±700.7	6091.6 ±699.8
24 h post-dose	5602.0 ±523.1	5366.8 ±808.4	5432.6 ±792.5	5877.6 ±951.2
RBC cholinesterase				
16 h pre-dose	11294.3 ±1597.5	9568.8 ±2033.1	11515.2 ±1453.0	10785.6 ±730.1
30 mins pre-dose	11749.5 ±1807.1	10345.2±1926.0	12102.0 ±1177.5	11173.8 ±1013.8
15 mins post-dose	12092.3 ±1158.1	10057.2 ±986.3	11656.2 ±1464.4	8978.4 ±1702.4
30 mins post-dose	11372.3 ±2122.6	8954.4 ±1537.6	10331.4 ±1184.8	7454.4 ±253.1
45 mins post-dose	11049.8 ±1285.8	9745.8 ±2441.4	9409.8 ±1599.0	7119.6 ±1267.5
1 h post-dose	10997.3 ±2267.7	8412.6 ±1318.6	8865.0 ±1266.2	7978.2 ±909.9
1 h 15 mins post-dose	11077.5 ±2151.6	7959.6 ±959.4	8522.4 ±1388.6	8044.8 ±1020.0
1 h 30 mins post-dose	11420.3 ±1142.1	8821.8 ±1384.6	8475.0 ±894.6	8416.8 ±780.0
1 h 45 mins post-dose	11683.5 ±1449.5	9467.4 ±1166.6	9140.4 ±444.6	8552.4 ±1556.5
2 h post-dose	12036.0 ±782.0	8972.4 ±1348.3	9843.0 ±511.8	9225.0 ±1197.0
3 h post-dose	12766.5 ±926.0	9731.4 ±2117.0	11616.6 ±1126.4	9651.0 ±2333.6
4 h post-dose	12716.3 ±1073.0	10424.0±2100.6	11475.0 ±833.2	10467.6 ±1532.6
6 h post-dose	12250.5 ±2561.9	9186.6 ±925.7	13508.4 ±1094.0	10789.8 ±1300.7
8 h post-dose	11193.8 ±3226.8	8752.2 ±1273.6	12880.8 ±1582.2	10948.2 ±1125.1
12 h post-dose	10914.8 ±2944.2	8212.2 ±582.7	13461.0 ±1162.3	10411.8 ±1791.3
24 h post-dose	11155.5 ±3277.6	9324.0 ±458.6	12946.8 ±1450.5	10843.8 ±1203.2

Data obtained from pp. 438-441, and 442-445, MRID 44721401.

3. **Increased salivation:** A comparison of group mean saliva weight at the various time points (excluding outliers) showed no dose response, except at one hour (control to high-dose: -13.5, 38.7, 50.3, and 60.3% [p=0.009] change from baseline (individual), respectively). However, data was not collected or reported for fluid intake after dosing which may have helped explain the difference in salivation at the one hour time point.

TABLE 4. Percent change from baseline of saliva weight as mean ± standard deviation over time for volunteers receiving methomyl (with and without outliers)

	Dosage group (mg/kg bw)							
	0 mg/kg		0.1 mg/kg		0.2 mg/kg		0.3 mg/kg	
Time	mean±SD	%change	mean±SD	%change	mean±SD	%change	mean±SD	%change
Saliva Weight								
1 h post-dose	2.28±1.29	-13.5±6.98	1.36±1.54	38.7±70.8	1.78±1.46	50.3±65.8	2.48±0.93	60.3±26.6*
2 h post-dose	2.00±0.95	-16.5±20.55	1.2±1.17	16.1±34.9	2.00±1.90	49.5±50.4*	1.58±0.68	1.10±29.2
3 h post-dose	1.68±0.63	-26.69±23.27	1.14±1.29	3.4±34.6	1.80±1.41	53.8±66.5*	1.52±0.43	-0.4±12.3
4 h post-dose	2.58±1.34	4.41±22.74	1.14±1.41	0.9±57.0	2.04±1.67	44.6±55.2	1.60±0.76	2.3±28.7
8 h post-dose	1.9±[illegible].20	-17.42±35.41	1.48±1.53	35.0±39.8	2.26±1.84	70.3±83.8**	1.44±0.82	-7.1±45.8
24 h post-dose	2.43±1.31	1.81±37.78	1.2±1.31	8.9±41.4	1.48±1.42	59.4±165.1	1.38±0.71	-10.8±26.9

*Statistically significant at $p < 0.05$, compared with controls (including outliers)
*Statistically significant at $p < 0.05$, compared with controls (excluding outliers)

4. **Pupillary size:** There were no significant differences in the changes from baseline in the initial pupil size, minimum pupil size, or recovery pupil size for any of the dose groups of methomyl compared with placebo.

B. **CLINICAL CHEMISTRY**: There were no statistical significant changes in any of the mean clinical chemistry indices with any dose of methomyl from -30 minutes to +24 hours.

Increased total bilirubin: On the individual level, three volunteers had total bilirubin concentrations above the normal range. One 0.1 mg/kg volunteer had increased total bilirubin at 30 minutes pre-dosing (31.4 µmol/L); one 0.2 mg/kg volunteer had increased total bilirubin values at screening (28.5 µmol/L), 30 minutes pre-dose (29.0 µmol/L), and 24 hours post-dosing (21.7 µmol/L); and one 0.3 mg/kg volunteer had increased total bilirubin values (clinical chemistry parameters for this individual were checked twice at screening), (42.2 and 47.4 µmol/L, respectively), 30 minutes pre-dose (47.3 µmol/L), and 24 hours post-dosing (56.9 µmol/L).

C. **BODY WEIGHT:** Body weight was not evaluated in this acute study.

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III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: "Under the conditions of this study and based on the absence of any clinical signs of cholinergic stimulation, ECG analysis, pulse, respiratory rate, or any statistical increases in salivation, pupillary responses, hematology, clinical chemistry, or statistically significant RBC or plasma ChE activities, the no-observed-adverse-effect-level (NOAEL) for humans after a single oral dose of methomyl is 0.1 $mg.kg^{-1}$ of body weight. "

B. EPA CONCLUSION:

No dose group had changes in pupillary size, respiratory rate, ECGs, vital signs, hematology, clinical chemistry, urinalysis, or clinical signs (with the exception of the 0.3 mg/kg individual who complained of a transient headache). A dose-response relationship was observed in all dose groups for plasma and RBC cholinesterase activity. In addition, cholinesterase activity for both plasma and RBC was consistent for timing of peak effect and time to recovery. Inhibition of ChE activity for both plasma and RBC ranged from -19% to -35% at the high dose (0.3 mg/kg) to -20% to -28% at the mid dose (0.2 mg/kg). RBC cholinesterase activity was decreased by 19% in the 0.1 mg/kg group (non-statistically) at 75 minutes post-dosing, which coincides with the timing of peak RBC cholinesterase inhibition of the mid- and high-dose groups. Plasma and RBC cholinesterase activity typically returned to normal by 6 hours post-dosing in all dose groups. Therefore, the NOAEL for humans after a single oral dose of methomyl is <0.1 mg/kg.

In addition, the Agency used the RBC ChE inhibition and recovery data for input into the Agency's BMDS model. The BMD_{10} is 0.040 mg/kg and $BMDL_{10}$ is 0.028 mg/kg. The BMD and BMDL estimates were considered for the *N*-methyl carbamate (NMC) cumulative risk assessment for refinement of the interspecies extrapolation factor for methomyl. Please refer to the cumulative risk assessment for details.

C. DEFICIENCIES: There were no study deficiencies identified that would have affected the outcome and conclusions of this study.

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