



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

JUN 30 1986

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MEMORANDUM

**SUBJECT:** Propetamphos; Safrotin EC; Response to Issues  
Presented in Laboratory Audit Report  
Project No. 1619  
Caswell No. 706A  
Record No. 168665

**FROM:** William Dykstra  
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**THRU:** Edwin Budd, Section Head  
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**TO:** William Miller  
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*Budd*  
*6/27/86*  
*W. Miller*  
*6/30/86*

Requested Action:

Review toxicology issues relating to lab audit of 2-year mouse study with propetamphos (WIL-79218).

Review:Issue #1:

The hepatocytic vacuolization among mid-and high-dose males in the study are compound-related findings.

Response #1:

Evaluation of liver findings presented in Table I shows that the NOEL of hepatocytic vacuolization is the low-dose of 1 mg/kg/day.

The NOEL was previously stated to be 6 mg/kg/day (mid-dose group) which was incorrect.

Issue #2:

The incidence of interstitial nephritis shows a dose-related effect across doses and a NOEL has not been established in both sexes of mice.

Response #2:

The Toxicology Branch believes that the incidence of interstitial nephritis (presented in Table II) demonstrates a NOEL at 1 mg/kg/day, for both sexes, the low-dose of the study. Although statistical evaluation yields a significant dose-response slope, the incidence of interstitial nephritis at the low-dose does not appear to be biologically significantly different between control groups I and II.

Issue #3:

The incidence of pulmonary tumors does not specify the number of tumor-bearing animals which have bronchoalveolar adenomas and/or carcinomas and bronchogenic carcinomas.

Response #3:

Table III presents the incidence of tumor-bearing animals with either bronchoalveolar adenomas or carcinomas. Mice which had both adenomas and carcinomas have been recorded only for carcinomas. Additionally, the incidence of pulmonary tumors observed is comparable between controls and treated groups.

Conclusion:

The lab audit report is correct with respect to the NOEL of the hepatocytic vacuolizations incidence in male mice. The previous NOEL was stated to be 6 mg/kg/day. Re-evaluation of the data indicates that the NOEL is 1 mg/kg/day (low-dose) for male mice for this effect.

Table I presents the observed incidence of hepatocytic vacuolization.

Similarly, Toxicology Branch believes that the low-dose of 1 mg/kg/day for both sexes is the NOEL for interstitial nephritis in the study. The previous NOEL was stated to be the mid-dose of the study.

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The incidence and distribution of pulmonary tumors in both sexes of mice are comparable between controls and treated groups.

Although the NOEL of the study has now been established at the low-dose (1mg/kg/day), the ADI for propetamphos is still 0.005 mg/kg/day.

The specific details of the re-evaluation of the study are attached.

Terminal sacrifice Control I

<u>No. Mice</u>	<u>14</u> <u>Males</u>	<u>27</u> <u>Females</u>
Bronchoalveolar adenoma	43, 19, <u>35</u> , 71	4, 8
Bronchoalveolar carcinoma	21, 29, 31, <u>35</u> , 105	24, 32, 96, 62

Terminal sacrifice Control II

<u>No. Mice</u>	<u>31</u> <u>Males</u>	<u>28</u> <u>Females</u>
Bronchoalveolar adenoma	233, 229, 253	224, 320
Bronchoalveolar carcinoma	223, 289, 313, 209 211, 241, 257, 295 221, 231, 317	214, 218, 308, 310 210, 230, 266

Terminal sacrifice Group IV

<u>No. Mice</u>	<u>21</u> <u>Males</u>	<u>26</u> <u>Females</u>
Bronchoalveolar adenoma	503, 521, 511, 535 <u>549</u>	0
Bronchoalveolar carcinoma	515, 561, 531, 551, 559, <u>549</u> , 565, 617	518, 606, 586, 526, 528, 552, 618
Bronchogenic carcinoma	0	558

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Terminal sacrifice Group V

<u>No. Mice</u>	28 <u>Males</u>	23 <u>Females</u>
Bronchoalveolar adenoma	725, <u>747</u> , 787, 793, <u>729</u> , 737, 739 757, 797	798, 716, 748 796, 740
Bronchoalveolar carcinoma	<u>747</u> , 711, 701	738, 714
Bronchogenic carcinoma	709	0

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Terminal sacrifice Group VI

<u>No. Mice</u>	29 <u>Males</u>	20 <u>Females</u>
Bronchoalveolar adenoma	901, 987, 939 953	940
Bronchoalveolar carcinoma	959, 909, 925, 961, 1005, 991, 931	948, 940, 902
Bronchogenic carcinoma	941	0

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Second Interim Sacrifice Control 1

<u>No. Mice</u>	<u>10</u> <u>Males</u>	<u>10</u> <u>Females</u>
Bronchoalveolar adenoma	0	90
Bronchoalveolar carcinoma	81, 101	86, 88

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Second Interim Sacrifice Control II

<u>No. Mice</u>	<u>10</u> <u>Males</u>	<u>10</u> <u>Females</u>
Bronchoalveolar adenoma	<u>259</u>	0
Bronchoalveolar carcinoma	<u>259</u> , 275	292
Bronchogenic carcinoma	0	274

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Second Interim Sacrifice Group IV

<u>No. Mice</u>	<u>10</u> <u>Males</u>	<u>10</u> <u>Females</u>
Bronchoalveolar adenoma	<u>579</u> , 581	0
Bronchoalveolar carcinoma	571, 573, 575 577, <u>579</u> , 593	566, 572

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Second Interim Sacrifice Group V

No. Mice	<u>10</u> <u>Males</u>	<u>10</u> <u>Females</u>
Bronchoalveolar adenoma	0	778
Bronchoalveolar carcinoma	773, 775, 777, 779	784

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Second Interim Sacrifice Group VI

No. Mice	<u>10</u> <u>Males</u>	<u>10</u> <u>Females</u>
Bronchoalveolar adenoma	975	1014
Bronchoalveolar carcinoma	979	982, 986

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First Interim Sacrifice Control Group I

No. Mice	<u>10</u> <u>Males</u>	<u>10</u> <u>Females</u>
Bronchoalveolar adenoma	0	144, 158
Bronchoalveolar carcinoma	151	150

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First Interim Sacrifice Control Group CII

No. Mice	<u>10 Males</u>	<u>10 Females</u>
Bronchoalveolar adenoma	345	0
Bronchoalveolar carcinoma	355	354, 356

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First Interim Sacrifice Group IV

No. Mice	<u>10 Males</u>	<u>10 Females</u>
Bronchoalveolar adenoma	651	0
Bronchoalveolar carcinoma	655	0

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First Interim Sacrifice Group V

No. Mice	<u>10 Males</u>	<u>10 Females</u>
Bronchoalveolar adenoma	827, 829	0
Bronchoalveolar carcinoma	0	0

First Interim Sacrifice Group VI

No. Mice	<u>10 Males</u>	<u>10 Females</u>
Bronchoalveolar adenoma	0	54
Bronchoalveolar carcinoma	49	0

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Non-Survivors Control Groups CI

No. Mice	<u>36 Males</u>	<u>23 Females</u>
Bronchoalveolar adenoma	25	106, 104
Bronchoalveolar carcinoma	65, 59 91, 7, 15	10, 34,
Bronchogenic carcinoma	0	72

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Non-Survivors Control Groups CII

No. Mice	<u>19 Males</u>	<u>22 Females</u>
Bronchoalveolar adenoma	0	208, 264
Bronchoalveolar carcinoma	227, 205	0

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Non-Survivors Groups IV

No. Mice	<u>29</u> <u>Males</u>	<u>23</u> <u>Females</u>
Bronchoalveolar adenomas	517, 541 589	544, 604
Bronchoalveolar carcinomas	609, 523, 611	560 532, 584
Bronchogenic carcinoma	557	0

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Non-Survivors Groups V

No. Mice	<u>12</u> <u>Males</u>	<u>17</u> <u>Females</u>
Bronchoalveolar adenomas	0	0
Bronchoalveolar carcinoma	705, 755, 733	750
Bronchogenic carcinoma	723	0

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Non-Survivors Groups VI

No. Mice	<u>21</u> <u>Males</u>	<u>30</u> <u>Females</u>
Bronchoalveolar adenoma	0	1002, 1016
Bronchoalveolar carcinoma	989, 937	58, 924, 954, 952
Bronchogenic carcinoma	1009	0

Histopathology

Control Group I

	<u>Males</u>	<u>Females</u>
No. terminal sacrifice	14	27
First interim sacrifice	10	10
Second interim sacrifice	10	10
<u>Non-survivors</u>	<u>36</u>	<u>23</u>
Total examined	70	70

Control Group II

No. terminal sacrifice	31	28
First interim sacrifice	10	10
Second interim sacrifice	10	10
<u>Non-survivors</u>	<u>19</u>	<u>22</u>
Total examined	70	70

Group IV 1 mg/kg/day

No. terminal sacrifice	21	26
First interim sacrifice	10	10
Second interim sacrifice	10	10
<u>Non-survivors</u>	<u>29</u>	<u>23</u>
Total examined	70	69

Group V 6 mg/kg/day

No. terminal sacrifice	28	23
First interim sacrifice	10	10
Second interim sacrifice	10	10
<u>Non-survivors</u>	<u>12</u>	<u>17</u>
Total examined	60	60

Group VI 21 mg/kg/day

No. terminal sacrifice	29	20
First interim sacrifice	10	10
Second interim sacrifice	10	10
<u>Non-survivors</u>	<u>21</u>	<u>30</u>
Total examined	70	70

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Table I Liver

<u>Dose (mg/kg/day)</u>	<u>CI</u>		<u>CII</u>		<u>1</u>		<u>6</u>		<u>21</u>	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
<u>No. Examined</u>	70	70	70	70	70	69	60	60	70	70
<u>Hepatocytic Vacuolization</u>	8	0	10	0	9	2	20	1	22	4

Table II Kidney

<u>Dose (mg/kg/day)</u>	<u>CI</u>		<u>CII</u>		<u>1</u>		<u>6</u>		<u>21</u>	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
<u>No. Examined</u>	70	70	70	70	70	69	60	60	70	70
<u>Interstitial Nephritis</u>	1	4	5	2	3	4	7	5	9	10

Table III Lung Tumors

<u>Dose (mg/kg/day)</u>	<u>CI</u>		<u>CII</u>		<u>1</u>		<u>6</u>		<u>21</u>	
	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>	<u>M</u>	<u>F</u>
<u>No. Examined</u>	70	70	70	70	70	69	60	60	70	70
<u>No. mice with Bronchoalveolar adenomas</u>	4	7	4	4	9	2	10	6	5	5
<u>No. mice with Bronchoalveolar carcinoma</u>	13	9	16	10	18	12	10	4	11	9
<u>No. mice with Bronchogenic carcinoma</u>	0	1	0	1	1	1	2	0	2	0
<u>Total</u>	17	17	20	15	28	15	22	10	18	14

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