MEMORANDUM

JAN 9 1997

SUBJECT: Carcinogenicity Peer Review of Chlorfenapyr (Pirate™)

FROM: Guruva B. Reddy, DVM, Ph.D. 
Review Section 4 
Toxicology Branch I 
Health Effects Division (7509C) 
and 
Esther Rinde, Ph.D. 
Manager, Carcinogenicity Peer Review Committee 
Science Analysis Branch 
Health Effects Division (7509C)

THROUGH: Stephanie R. Irene Ph.D. 
Deputy Director, Health Effects Division (7509C)

TO: Dennis Edwards 
Product Manager #19 
Insecticide-Rodenticide Branch 
Registration Division (7505C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on September 25, 1996 to discuss and evaluate the weight-of-the-evidence on Chlorfenapyr with particular reference to its carcinogenic potential.

In accordance with the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10, 1996), Chlorfenapyr was characterized as "cannot be determined, suggestive", based on increases in tumors in the rat only, which were not considered to be persuasive but could not be dismissed.
SUMMARY

Administration of Chlorfenapyr in the diet to Charles River CD:BR (Sprague-Dawley) rats at doses up to 600 ppm for 2 years was associated with increases in liver adenomas and combined adenoma/carcinoma (due mainly to the adenomas), malignant histiocytic sarcomas and testicular interstitial cell tumors in males and in uterine polyps at the highest dose in females. All these tumor increases occurred with statistically significant positive trends, but without pairwise significance (for malignant histiocytic sarcomas p=0.056), when compared to concurrent controls. The incidences at the highest dose for the liver adenomas, testicular interstitial cell tumors, and histiocytic sarcomas in male rats exceeded or slightly exceeded the maximal incidence of historical controls. The highest dose in this study was considered to be adequate, but not excessive, in both sexes based on weight gain depressions >10%, without accompanying signs of toxicity.

Administration of Chlorfenapyr in the diet to Swiss Crl:CD-1(ICR) BR mice at doses up to 240 ppm for 80 weeks was not associated with any increase in tumor incidence in any tissue. The highest dose was considered by the CPRC to have been excessive in both sexes based on central nervous system (CNS) lesions and decreased survival in female mice. The CPRC agreed however that the study was adequate, with adequate dose spacing.

Chlorfenapyr was tested in a variety of mutagenicity assays and does not appear to have mutagenic activity. Chlorfenapyr is a member of a new class of chemicals known as pyrrole, for which no structure-activity correlations could be proposed.

The consensus of the CPRC to characterize the weight of evidence for Chlorfenapyr as "cannot be determined, suggestive" was based on the absence of persuasive evidence; increases in tumors occurred with significant positive trends only, mainly at the highest dose and only in rats. There was also no apparent concern for mutagenic activity and a lack of structure-activity data.
A. Individuals in Attendance at the meetings:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

William Burnam
Karl Baetcke
Marion Copley
Elizabeth Doyle
Clark Swentzel
for Yiannakis Ioannou
Hugh Pettigrew
Esther Rinde

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Guruva Reddy¹
Lori Brunsman
Lucas Brennecke²
(PAI/ORNL)

3. Other Attendees:

Catherine Biden, Joycelyn Stewart

¹Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

²Signature indicates concurrence with pathology report.
B. Material Reviewed

The material available for review consisted of DER's, one-liners, data from the literature and other data summaries prepared and/or supplied by Dr. Guruva Reddy, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background Information:

Chlorfenapyr [4-bromo-2-(4-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-1H-pyrrole-3-carbonitrile] is an insecticide-miticide for use on cotton, vegetables, citrus and ornamentals. It is manufactured by American Cyanamid Company and proposed to be sold under the trade names of PIRATE 3SC Insecticide-Miticide or AC303,630 3SC Insecticide-Miticide (32% a.i.) and ALERT 2SC Insecticide-Miticide or AC303,630 2SC Insecticide-Miticide (21% a.i.).

Chlorfenapyr is a white solid with a melting point of 100-101°C. It is soluble 0.12 mg/ml in deionized water and 7.09 g/100 ml in methanol at 25°C.

The Chemical Abstracts Registry Number (CAS No.) is 122453-73-0; the P. C. Number is 129093.

The Reference Dose (RfD) for Chlorfenapyr is 0.003 mg/kg/day based on a NOEL of 6 mg/kg/day in a chronic toxicity mice feeding study. The uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability; an additional modifying factor of 10 was added because of the type of lesions, the lack of understanding of their cause, and possible further unknown toxicity with regard to the developing young. The chemical has not been previously reviewed by the Cancer Peer Review Committee (CPRC).

The chemical structure of Chlorfenapyr is:

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\begin{center}
\includegraphics[width=0.5\textwidth]{chlorfenapyrstructure.png}
\end{center}
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D. Evaluation of Carcinogenicity Evidence:

1. Crl:CD BR Rat Carcinogenicity Study


a. Experimental Design

Chlorfenapyr (94.5%) was administered in the diet to groups of 55 male and 55 female Crl:CD BR rats at concentrations of 0 (control), 60, 300 or 600 ppm for 2 years, equivalent to an intake of approximately 0, 2.9, 15.0, or 30.8 mg/kg/day, in males and 0, 3.6, 18.6 or 37.0 mg/kg/day, in females, respectively. There were an additional 10 rats/sex/group on study sacrificed at 52 weeks. The age of animals were 6 weeks and their body weights were 168-248 gm (males) and 150-208 gm (females) at the study initiation.

b. Discussion of Tumor Data

In males at the HDT (600 ppm), malignant histiocytic sarcomas increased significantly (p < 0.05) over controls by life-table analysis; there was also increased incidence of malignant lymphocytic lymphoma compared to controls, but not significant by Fisher’s exact test or life table methods. Male rats also had significant increasing trends in hepatocellular adenomas, and hepatocellular adenomas and/or carcinomas combined by Exact trend test, at p < 0.05. In female rats (600 ppm), endometrial stromal polyps increased significantly (p < 0.05) when analyzed by Fisher’s exact test.

Censored tumor incidences in male rats are presented in Tables 1, 2 and 3 and in female rats in Tables 4 and 5. Noncensored data, for the purpose of comparison to historical control data, are presented in Table 6. Historical control values for the incidence of selected tumors in rats at the testing facility and Charles River Laboratory are given in Table 7. The male rat data were analyzed using Exact trend test for trends and the Fisher’s Exact test for pair-wise comparisons. The female rat data were analyzed based upon Peto’s Prevalence Test since there was a statistically significant negative trend for mortality with increased doses.
MALES

Hepatocellular adenomas and carcinomas: Male rats had significant increasing trends in hepatocellular adenomas, adenomas and/or carcinomas combined by Exact trend test, at p < 0.05 (Table 1). The uncensored incidence (Table 6) of adenomas of 4.6% (3/65) at 600 ppm is above the maximal historical spontaneous incidence at the testing facility of 3.3% (Attachment 1 - File copy) and the Charles River Laboratory of 4.2%. The uncensored combined incidence of adenomas and carcinomas of 7.7% (5/65) at the highest dose tested (HDT) is above the mean incidence at the testing facility based on ten studies (3.9%, ranges: 1.3% to 8%) and below the maximal incidence published by Charles River Laboratories (27.3%; Table 7).

Malignant histiocytic sarcoma and malignant lymphocytic lymphoma: Male rats had a significant increasing trend in malignant histiocytic sarcomas (p < 0.05; Table 2). The incidence of malignant histiocytic sarcoma of 8% is above the maximal incidence of 5.6% for the testing facility and 7.1% for the Charles River Laboratories (2/1992). (Originally, malignant lymphomas were combined with malignant histiocytic sarcomas, but it was determined that it is inappropriate to combine them because of different origins.)

Testicular Interstitial cell tumors: Male rats had increasing trends in interstitial cell tumors at p < 0.05 (Table 3). The uncensored incidence (Table 6) of 10.8% (7/65) is slightly above the maximal incidence of 10% (mean = 3.5%) for the testing facility, and 10% at the Charles River Laboratory.

FEMALES

Mammary fibroadenomas and carcinomas: Analysis did not establish trends. There were significant differences in the pair-wise comparisons of 60 ppm group for fibroadenomas (p < 0.05; Table 4). The uncensored incidence of fibroadenoma at the 0, 60, 300 or 600 ppm was 43%, 71, 46% or 30%, respectively (Table 6) and was below (except at 60 ppm) the maximal spontaneous incidence for this tumor at the testing facility of 65% and at the Charles River Laboratory of 49%. The uncensored incidence (Table 6) of carcinoma in the 300 ppm group of 35% is above the mean of 11.4 (maximal incidence of 28.3%) for the testing facility and the maximal incidence of 31.4% for the Charles River Laboratory.

Uterine endometrial stromal polyps: Female rats had a significant increasing trend in uterine endometrial stromal polyps at p < 0.05
(Table 5). There were no significant differences in the pair-wise comparisons of the dosed groups with the controls for uterine endometrial stromal polyps. The uncensored incidence (Table 6) of 7.7% (5/65) is above the mean of 4.8% (maximal incidence of 13.3%) for the testing facility and the mean of 4.05% (maximal incidence of 10%) for the Charles River Laboratory.
Table 1. Pirate - Sprague-Dawley Crl:CD BR Rat Study

Male Liver Tumor Rates* and Exact Trend Test
and Fisher's Exact Test Results (p values)

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>0</th>
<th>60</th>
<th>300</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomas</td>
<td>(%)</td>
<td>(0)</td>
<td>(0)</td>
<td>(6)</td>
</tr>
<tr>
<td></td>
<td>0/51</td>
<td>0/55</td>
<td>3*/54</td>
<td>3/50</td>
</tr>
<tr>
<td>p</td>
<td>0.022*</td>
<td>1.000</td>
<td>0.132</td>
<td>0.118</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>(%)</td>
<td>(6)</td>
<td>(0)</td>
<td>(4)</td>
</tr>
<tr>
<td></td>
<td>3/51</td>
<td>0/55</td>
<td>2*/54</td>
<td>2/50</td>
</tr>
<tr>
<td>p</td>
<td>0.421</td>
<td>0.108a</td>
<td>0.473</td>
<td>0.510</td>
</tr>
<tr>
<td>Combined</td>
<td>(%)</td>
<td>(6)</td>
<td>(0)</td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>3/51</td>
<td>0/55</td>
<td>5/54</td>
<td>5/50</td>
</tr>
<tr>
<td>p</td>
<td>0.045*</td>
<td>0.108a</td>
<td>0.390</td>
<td>0.346</td>
</tr>
</tbody>
</table>

*Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54. Also excludes week 53 interim sacrifice animals.

*First adenoma observed at week 105, dose 300 ppm.

*First carcinoma observed at week 88, dose 300 ppm.

*Negative change from control.

*Reproduced from Qualitative Risk assessment review

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level.

If *, then p < 0.05. If **, then p < 0.01.
Table 2. Chlorfenapyr - Sprague-Dawley Crl:CD BR Rat Study

Male Malignant Histiocytic Sarcoma Tumor Rates* and Exact Trend Test and Fisher’s Exact Test Results (p values)

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>0</th>
<th>60</th>
<th>300</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histiocytic Sarcomas</td>
<td>0/51</td>
<td>1/55</td>
<td>1/54</td>
<td>4*/50</td>
</tr>
<tr>
<td>(%)</td>
<td>(0)</td>
<td>(2)</td>
<td>(2)</td>
<td>(8)</td>
</tr>
<tr>
<td>p</td>
<td>0.012*</td>
<td>0.519</td>
<td>0.514</td>
<td>0.056</td>
</tr>
</tbody>
</table>

*Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54 for histiocytic sarcomas. Also excludes week 53 interim sacrifice animals.

*First histiocytic sarcoma observed at week 58, dose 600 ppm.

Reproduced from Qualitative Risk Assessment review
Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

If *, then p < 0.05. If **, then p < 0.01.
Table 3. Chlorfenapyr - Sprague-Dawley Crl:CD BR Rat Study

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>0</th>
<th>60</th>
<th>300</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial Cell Tumors (%)</td>
<td>3/51</td>
<td>1*/55</td>
<td>3/54</td>
<td>7/50</td>
</tr>
<tr>
<td>p =</td>
<td>0.019*</td>
<td>0.281*</td>
<td>0.633</td>
<td>0.151</td>
</tr>
</tbody>
</table>

*Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54. Also excludes week 53 interim sacrifice animals.

aFirst interstitial cell tumor observed at week 84, dose 60 ppm.

"Negative change from control.

\textsuperscript{a}Reproduced from Qualitative Risk Assessment review.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then p < 0.05. If **, then p < 0.01.
Table 4. Chlorfenapyr - Sprague-Dawley Crl:CD BR Rat Study

Female Mammary Gland Tumor Rates* and Peto's Prevalence Test Results (p values)

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>0</th>
<th>60</th>
<th>300</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>27/52</td>
<td>35/50</td>
<td>24/46</td>
<td>19a/55</td>
</tr>
<tr>
<td>Fibroadenomas (%)</td>
<td>(52)</td>
<td>(70)</td>
<td>(52)</td>
<td>(35)</td>
</tr>
<tr>
<td>p =</td>
<td>0.9995a</td>
<td>0.024*</td>
<td>0.440</td>
<td>0.992a</td>
</tr>
<tr>
<td>Carcinomas 11/52</td>
<td>12/50</td>
<td>16/46</td>
<td>15b/55</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td>(21)</td>
<td>(24)</td>
<td>(35)</td>
<td>(27)</td>
</tr>
<tr>
<td>p =</td>
<td>0.227</td>
<td>0.451</td>
<td>0.053</td>
<td>0.225</td>
</tr>
</tbody>
</table>

*aFirst fibroadenoma observed at week 60, dose 600 ppm.

*bFirst carcinoma observed at week 60, dose 600 ppm.

"Negative change from control.

"Reproduced from Qualitative Risk Assessment review

Note: One animal in the control group and two animals in the 60 ppm dose group of the interim sacrifice group had mammary gland fibroadenomas. Two animals in the 300 ppm dose group and one animal in the 600 ppm dose group of the interim sacrifice group had mammary gland carcinomas. Interim sacrifice and accidental death animals are not included in this analysis.

Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level.

If *, then p < 0.05. If **, then p < 0.01.
Table 5. Chlorfenapyr - Sprague-Dawley Crl:CD BR Rat Study

Female Uterine Tumor Rates* and Exact Trend Test
and Fisher's Exact Test Results (p values)

<table>
<thead>
<tr>
<th>Dose (ppm)</th>
<th>0</th>
<th>60</th>
<th>300</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endometrial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stromal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyps (%)</td>
<td>0/19</td>
<td>0/7</td>
<td>0/8</td>
<td>54/30</td>
</tr>
<tr>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td></td>
<td>(17)</td>
</tr>
<tr>
<td>p =</td>
<td>0.019*</td>
<td>-</td>
<td>-</td>
<td>0.075</td>
</tr>
</tbody>
</table>

*Number of tumor bearing animals/Number of animals examined at the terminal sacrifice.

*Endometrial stromal polyps were only observed at week 105 in terminally sacrificed animals at the 600 ppm dose group.

*Reproduced from Qualitative Risk Assessment review

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Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then p < 0.05. If **, then p < 0.01.
TABLE 6. UNCENSORED INCIDENCE OF TUMORS IN RATS (ALL DISPOSITIONS)\textsuperscript{A}.

<table>
<thead>
<tr>
<th>Tumors</th>
<th>Number Lesions/Organs Examined</th>
<th>Concentration in Diet (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td></td>
<td>0  60  300  600</td>
<td>0  60  300  600</td>
</tr>
<tr>
<td>Uterus Endometrial Stromal Polyp</td>
<td>0/65 0/45 0/39 5/65*</td>
<td>17% 23% 35% 25%</td>
</tr>
<tr>
<td>Mammary Carcinoma</td>
<td>11/65 12/52 18/52 16/64</td>
<td></td>
</tr>
<tr>
<td>Mammary Fibroadenoma</td>
<td>28/65 37/52 24/52 19/64</td>
<td></td>
</tr>
<tr>
<td>Liver Hepatocellular Adenoma</td>
<td>0/65 0/65 3/65 3/65</td>
<td>1/65 0/65 0/65 0/65</td>
</tr>
<tr>
<td>Liver Hepatocellular Adenomas/Carcinomas</td>
<td>3/65 0/65 5/65 5/65</td>
<td>1/65 0/65 0/65 0/65</td>
</tr>
<tr>
<td>Malignant Histiocytic Sarcoma (multiple sites)</td>
<td>0/65 1/65 1/65 4/65*</td>
<td>2/65 0/65 0/65 0/65</td>
</tr>
<tr>
<td>Malignant Lymphocytic Lymphoma</td>
<td>1/65 2/65 0/65 5/65</td>
<td>2/65 1/65 2/65 0/65</td>
</tr>
<tr>
<td>Testis Benign Interstitial Cell Tumor</td>
<td>3/65 1/22 3/32 7/65</td>
<td></td>
</tr>
</tbody>
</table>

Data obtained from Table 15A-D, pages 284-361, and Appendices 13A-C, in the study report.
\* Significantly different from control at p ≤0.05; Fisher exact test.
\textsuperscript{A} This noncensored data is for comparison only with historical control data, not for statistical analysis.
TABLE 7. HISTORICAL CONTROL VALUES

<table>
<thead>
<tr>
<th></th>
<th>CHARLES RIVER LABORATORY 1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MALES</td>
<td></td>
<td>FEMALES</td>
</tr>
<tr>
<td>Tumor type</td>
<td>Minimum (%)</td>
<td>Maximum (%)</td>
<td>Mean (%)</td>
</tr>
<tr>
<td>Hepatocellular Adenomas</td>
<td>1.3</td>
<td>18.2</td>
<td>4.21</td>
</tr>
<tr>
<td>Hepatocellular Carcinomas</td>
<td>1.1</td>
<td>9.1</td>
<td>2.62</td>
</tr>
<tr>
<td>M. histiocytic sarcoma</td>
<td>1.4</td>
<td>7.1</td>
<td>1.63</td>
</tr>
<tr>
<td>M. lymphocytic lymphoma</td>
<td>1.4</td>
<td>2.9</td>
<td>0.48</td>
</tr>
<tr>
<td>Interstitial</td>
<td>1.4</td>
<td>10.0</td>
<td>4.68</td>
</tr>
</tbody>
</table>

HAZLETON WASHINGTON, INC. (TESTING FACILITY)

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular Adenomas</td>
<td>0</td>
<td>3.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Hepatocellular Carcinomas</td>
<td>0</td>
<td>8.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Liver Adenomas + Carcinomas</td>
<td>1.3</td>
<td>8.0</td>
<td>3.9</td>
</tr>
<tr>
<td>M. histiocytic sarcoma</td>
<td>0</td>
<td>5.6</td>
<td>1.3</td>
</tr>
<tr>
<td>M. lymphocytic lymphoma</td>
<td>0</td>
<td>3.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Interstitial</td>
<td>1.4</td>
<td>10.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

c. Non-neoplastic Lesions

In this study, liver was the target organ for Chlorfenapyr toxicity. The incidence and severity of hepatocellular lesions, characterized as centrilocular to midzonal hepatocellular enlargement, increased significantly (P < 0.05) in both sexes at 300 and 600 ppm levels. These changes occurred in rats at the interim, unscheduled and terminal sacrifices. The overall incidence of these lesions in the 0, 60, 300 and 600 ppm groups was 5, 2, 26 and 72%, respectively, in males and 9, 2, 27, and 83%, respectively, in females.
No significant increase in mortality occurred in either sex. The overall survival rate, ranged from 47 - 56% in males and 27 - 49% in females.

Males and females at the HTD (600 ppm) had significantly decreased body weights starting at week 3 of the study. By week 105, only females exhibited significant decreases in body weights. At week 105, HDT males and females had mean body weight reductions of 6.8% and 18%, respectively. In both sexes of the 300 ppm group, mean body weight depressions frequently reached statistical significance (p < 0.05) from week 4 in females and from week 8 in males. By the end of the study, the mean body weights of males and females were depressed 5.7% and 16.8%, respectively, compared to controls. The mean body weights of both sexes at 60 ppm were comparable to the controls throughout the study.

Statistically significant (p < 0.05) dose-related decreases in weekly body weight gains occurred frequently in the 300 and 600 ppm groups of both sexes during the first year of treatment; there were only occasional decreases in the last half of the study. By the end of the first year at 300 ppm, males and females had decreased weight gains of 6% and 10%, respectively; and at 600 ppm, 12% and 22%, respectively, compared to controls. By the end of the study, only mid-and HDT females had significant (p < 0.05) cumulative body weight gains reductions of 26% and 29%, respectively, compared to controls.

Males at the HDT had reduced food efficiency, decreased RBC counts, decreased HCT, decreased HGB, increased reticulocyte counts, increased serum globulin, and increased relative liver weights. HDT females had decreased food consumption and efficiency, increased cholesterol, increased globulin, and increased relative liver weights. At 52 weeks, males in the 300 and 600 ppm groups had increased relative liver weights of 2.67% and 2.88%, respectively, compared to the 2.34% for the controls; and in females for 3.03% and 3.28%, respectively, compared to the 2.53% for the controls. At terminal sacrifice HDT males and females had significantly increased relative liver weights of 3.3% vs 2.65 (control) and 3.55% vs 2.81 (control), respectively.

The NOEL for systemic toxicity was 60 ppm. The LOEL for systemic toxicity was 300 ppm, based on decreased body weights and weight gains, increased relative liver weights associated with centrilobular to midzonal or diffuse hepatocellular enlargement in both sexes.
d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Doses for this study were based on findings from previous studies which used the same dose levels. In a one-generation pilot reproduction study (MRID 434292835), Chlorfenapyr (94.5%) was administered in diet to albino rats (10/sex/group) at 0, 60, 300, or 600 ppm. Body weight was depressed 12.6% during the pre-mating period in 300 ppm group. At 600 ppm, body weight was depressed 13 - 15% during the pre-mating period. Similarly in a 2-generation reproduction study (MRID 43492836), the 300 ppm P₁ and P₁ female pre-mating body weight gains were depressed 4.6% and 5.4%, respectively. HDT P₁ and P₁, male, pre-mating body weight gains were depressed 11% and 12%, respectively; and in HDT P₁ and P₁ females, pre-mating weight gains were depressed 9% and 15%, respectively, compared to controls.

There was systemic toxicity at 300 ppm in both sexes. At this dose level, there was: 1) decreased body weights and weight gains (cumulative weight gains females - 26%); 2) increased relative liver weights; and 3) centrilobular to midzonal hepatocellular enlargement.

The mid dose level (300 ppm) for males and females for this study was considered adequate based on decreased body weights and weight gains, increased relative liver weights and associated hepatocellular enlargement. Toxicity was considered adequate but not excessive at the high dose.

2. 80-Week Swiss Crl:CD-1(ICR) BR Mice Carcinogenicity Study

Reference: L. Bernier (1994); A Chronic Dietary Toxicity and Oncogenicity Study with AC 303,630 in Mice; Testing Facility - Bio-Research Laboratories, Ltd., Senneville, Quebec, Canada; Laboratory project ID 84580; MRID No. 43492838.

a. Experimental Design

Chlorfenapyr (94.5%) was administered in the diet to groups of 65 male and 65 female Swiss Crl:CD-1(ICR)BR mice for 80 weeks at concentrations of 0 (control), 20, 120 or 240 ppm, equivalent to an intake of 0, 2.8, 16.6, or 34.5 mg/kg/day, respectively, in males and 0, 3.7, 21.9, or 44.5 mg/kg/day, respectively, in females. There were an additional 10 mice/sex/group on study were sacrificed at 52 weeks. The age of animals were 6 weeks and their body weights were 20.6 - 27.0 gm (males) and 17.2 - 21.9 gm (females) at study initiation. Animals were housed individually and received food and water ad libitum.
b. Discussion of Tumor Data

Administration of Chlorfenapyr did not result in an increase in tumor incidence in any tissue. Table 8 summarizes the more common neoplastic lesions in this study.

### TABLE 8. INCIDENCE OF NEOPLASTIC LESIONS OF LIVER AND LUNGS

<table>
<thead>
<tr>
<th>Organ/Neoplasm</th>
<th>0</th>
<th>20</th>
<th>120</th>
<th>240</th>
<th>Concentration in Diet (ppm)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>20</td>
<td>120</td>
<td>240</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver:</td>
<td>(65)*</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
</tr>
<tr>
<td>Adenoma</td>
<td>8</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung:</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
<td>(65)</td>
</tr>
<tr>
<td>A/B Adenoma</td>
<td>16</td>
<td>12</td>
<td>13</td>
<td>10</td>
<td>7</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>A/B Carcinoma</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* Number of tissues examined.

Data extracted from Study No. 84580 (MRID 43492838) Table No. 23, p 190-194.

c. Non-neoplastic Lesions

In this study, the central nervous system (CNS) and integumentary system were the target organs for Chlorfenapyr toxicity. The incidence of CNS vacuolation (brain, spinal cord and optic nerve) was significant and dose-related. The incidence of brain vacuolation increased significantly in the 120 and 240 ppm males and females after the first year of the study. The overall incidence (including interim sacrifices) of CNS vacuolation was 4/65, 3/65, 14/55, and 49/65 in males and 10/65, 5/65, 28/65 and 58/65 in females from groups 0, 20, 120 or 240 ppm, respectively. Generally, HTD (240 ppm) animals had vacuolation in the white matter of the corpus callosum, tapetum, hippocampus and cerebellum.

Vacuolation was observed less frequently in the spinal cord, particularly thoracic and cervical areas. HTD males and females had increased incidence of vacuoles in the spinal cord and optic nerve. Other non-neoplastic lesions (bone marrow myelopoiesis in males and histiocytosis of the lung and lachrymal gland in females)
that reached statistical significance at the 240 ppm, may not be biologically relevant.

At 240 ppm in males, and to a lesser extent in HTD females, the incidences of skin ulceration and scabbing, and in 120 ppm males skin scabbing increased pre-terminally. Mice sacrificed at 52 weeks were not affected.

Overall mortality was statistically (p < 0.05) increased compared with controls in the 240 ppm female group. Most of the deaths in this group occurred after the first year of treatment. Percent of survival were 75, 75, 71, and 78 for males and 80, 71, 73, and 60 for females at 80 weeks in 0, 20, 120, and 240 ppm groups, respectively. The survival rates far exceeded the guideline requirement of not less than 25%. Historical control data on % survival from this testing facility for CD-1 female mice was 75, based on three 18-month oncogenicity studies (1988 to 1991).

On Day 0, males in the 20 ppm and 240 ppm groups had significantly lower body weights and this difference increased in the 240 ppm males during the study. Among the females, occasionally the mean body weights decreased (p < 0.05) from week 1 in HDT animals and from week 16 in animals receiving 120 ppm. By week 30 in 120 ppm females and week 34 in 240 ppm females the decrease in mean body weights were statistically significant compared to controls on almost all occasions throughout the end of the study. Overall HDT males and females and 120 ppm females had lower growth rates. Between weeks 0 and 13 mean weight gains in males at 240 ppm were 84% of the controls. Overall mean body weight gain in HDT males and females was 23% and 21% lower than the controls by the end of the study; in 120 ppm females weight gain was 12% less than controls.

Food consumption was marginally decreased in males between weeks 0 and 13 in 240 ppm group (96.6% of controls) and between weeks 13 and 26 in 120 ppm group (97.7% of control) and during the study in 240 ppm group (96.5% of control). In females, overall food consumption during weeks 1 -13 was 5 - 8% greater in the dosed groups than in controls.

No significant compound-related effects were observed in ophthalmological or hematologic parameters. At terminal sacrifice, absolute kidney weights of HDT males decreased 19% (p < 0.05), but the kidney to body weight ratio was not affected suggesting that the effect was related to the decrease in mean body weight. There was no time or treatment-related effect on the absolute liver weight or liver to body weight ratios. Based on the above and CNS
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lesions, the NOEL for systemic toxicity was 20 ppm and the LOEL was 120 ppm.

d. **Adequacy of Dosing for Assessment of Carcinogenic Potential**

Selection of species and dietary concentrations for the carcinogenicity testing of Chlorfenapyr in mice was based on the results of a 13-week oral toxicity test conducted using male and female CD-1 mice (MRID No. 43492830). In the 13-week oral toxicity test, mice were administered Chlorfenapyr in the diet at concentrations of 0, 40, 80, 160, or 320 ppm, equivalent to 0, 7.1, 14.8, 27.6 or 62.6 mg/kg/day, respectively, for males and 0, 9.2, 19.3, 40.0 or 78 mg/kg/day, respectively, for females. One male mice at 80 ppm, and one male and female in the 160 or 320 ppm exhibited toxic response; two mice in 320 ppm group died 2 days after feeding. HDT males and females had depressed body weights of 26% and 29%, respectively, compared to controls. Relative liver weights and spleen weights were increased in 160 or 320 ppm males and relative liver weights in 320 ppm females. Hepatocellular hypertrophy was dose-related in males and females. In males, it was 30% in the 80 ppm, 65% in the 160 ppm, and 95% in the 320 ppm groups; in females, 0% in 80 ppm, 20% in 160 ppm and 50% in 320 ppm groups. Spongiform encephalopathy was noted in the brain and spinal cord of 90 - 95% of both males and females in 320 ppm group.

In this 80-week carcinogenicity study, based on the decreased survival of HDT females by 40%, increased incidence of CNS lesions and decreased body weight gains in males and females of 120 and 240 ppm groups, and skin lesions in both sexes at 240 ppm, the dose levels used are considered adequate for testing the carcinogenic potential of Chlorfenapyr. This conclusion is supported by the recent evaluation (7/18/96) of this study by the Health Effects Division's RfD/Peer Review Committee which determined the dose levels of this study to be adequate for testing the carcinogenic potential of Chlorfenapyr.
E. Additional Toxicology Data on Chlorfenapyr:

1. Metabolism

An acceptable metabolism study in Sprague-Dawley rat was submitted (MRID No. 43492844). The study indicates that following oral administration of ¹⁴C-Chlorfenapyr at 20 mg/kg/day (labeled 2-pyrrole-¹⁴C ring or phenyl-¹⁴C ring) in rats, Chlorfenapyr is poorly absorbed. The radioactivity in urine from the high dosed rats was about half that from the single and multiple-low dosed rats. Approximately 80% of the dose was eliminated in the feces; most of the radioactivity was recovered in urine and feces within 48 hours after dosing. Female rats had twice the amount of radioactivity in carcass, blood and fat than the male rats. After 7 days, 89 - 121% of radioactivity was recovered. Liver had the highest recovery of radioactivity (0.15 - 0.48% of the dose).

Metabolite extraction accounted for 72-91% of the administered dose. Parent was the major radioactive compound found in the excreta and accounted for = 40 - 70% of the administered dose. Minor amounts of eight (8) primary and conjugated metabolites and four unidentified components were detected, each at less than 10% of the dosed radioactivity. Liver and kidney contained several primary and conjugated metabolites and only minor levels of the parent compound (< 8.3% of the radioactivity in the sample).

Major metabolic pathways for the compound include the following:

1) Major disposition route of orally administered compound is fecal excretion of unaltered compound, and

2) Cleavage of the ethoxymethyl side-chain, followed by de-alkylation and ring hydroxylation, and some degree of conjugation of the de-alkylated, ring-hydroxylated metabolite.

2. Mutagenicity

Chlorfenapyr was negative in the following acceptable studies:

a) In vitro point mutation assays, both mammalian (Chinese hamster ovary cells) (MRID No. 42770224/43187601) and bacterial (S. typhimurium/E. coli) (MRID No. 42770223) with and without S-9 activation systems.

b) Unscheduled DNA synthesis (UDS) in primary rat hepatocytes assaying for DNA repair in response to DNA damage (MRID No.
42770226).

c) Chromosomal aberrations tests using CHO cells (MRID No. 434928443) and chinese hamster lung fibroblasts (MRID No. 43492839) and a micronucleus assay in CD-1 mice (MRID Nos. 42770225/43187602).

d) Three possible metabolites were tested in Salmonella and E. coli for gene mutations and were found to be negative (MRID Nos. 43492840, 43492841, 43492842).

3. Structure-Activity Correlations

Chlorfenapyr is a member of a new class of chemicals known as pyrrole. Therefore, no structure-activity correlations can be proposed (Dr. Alberto Protzel). Chlorfenapyr acts by uncoupling pests' mitochondrial oxidative phosphorylation through an electrochemical gradient.
F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on Chlorfenapyr in a weight-of-the-evidence determination of carcinogenic potential.

1. Chlorfenapyr when administered in the diet (0, 60, 300 or 600 ppm for 2 years) to male and female Crl:CD BR rats, was associated with significant (p < 0.05) increasing trends in hepatocellular adenomas, hepatocellular adenomas and/or carcinomas combined, malignant histiocytic sarcomas (multiple sites), and testicular interstitial cell tumors in male rats. The uncensored incidence of adenomas of 4.6% at 600 ppm is above the maximal historical spontaneous incidence at the testing facility of 3.3% and the Charles river Laboratory of 4.2%. The uncensored combined incidence of adenomas and carcinomas of 7.7% at HDT is above the mean incidence at the testing facility of 3.9% and below the maximal incidence of 27.3% at Charles River Laboratories. The uncensored incidence of malignant histiocytic sarcoma of 8% is above the maximal incidence of 5.6% for the testing facility and 7.1% for the Charles River Laboratory. The uncensored incidence of testicular interstitial cell tumors of 10.8% is slightly above the maximal incidence of 10% at the testing facility and 10% at the Charles River Laboratory.

In female rats at the HDT (600 ppm) there was a statistically significant increasing trend in the endometrial stromal polyps. There were no trends for mammary gland fibroadenomas and carcinomas. There was a significant difference in pair-wise comparison of fibroadenomas at 60 ppm. The fibroadenomas at the 0, 60, 300 or 600 ppm (uncensored data) was 43%, 71%, 46% or 30%, respectively, below (except at 60 ppm) the maximal spontaneous incidence for this tumor at the testing facility of 65% and at the Charles River Laboratory of 49%. The incidence of carcinomas in the 300 ppm group was 35%, above the mean of 11.4 (maximal incidence of 28.3%) for the testing facility and the maximal incidence of 31.4% for the Charles River Laboratory. The incidence of uterine endometrial stromal polyps of 7.7% is above the mean of 4.8% (maximal incidence of 13.3%) for the testing facility and the mean of 4.05% (maximal incidence of 10%) for the Charles River Laboratory.

2. Chlorfenapyr, when administered in the diet (0, 20, 120, and 240 ppm for 80 weeks) to Swiss Crl:CD-1(ICR)BR mice, was not associated with any increased tumor incidence in either males or females.

3. There is no evidence that Chlorfenapyr has genotoxic potential.

4. Chlorfenapyr is a member of new class of chemicals known as pyroles. No analogs have been identified to compare for the tumorigenic potential.
G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the EPA proposed Guidelines for Carcinogenic Risk Assessment (April 10, 1996) for classifying the weight of evidence for Chlorfenapyr.

The overall evidence in animals was not persuasive, but could not be dismissed. Increases in tumors in rats occurred with significant positive trends only, and mainly at the highest dose. Chlorfenapyr was not associated with increases in tumors in mice and, there was no apparent concern for mutagenic activity and an absence of structure-activity data. There is no human data for Chlorfenapyr. The CPRC concluded that the evidence for Chlorfenapyr should be characterized as "cannot be determined - suggestive".