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

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

TXR No.: 0054822

MEMORANDUM

DATE: February 14, 2008

SUBJECT: **PYRETHRINS:** Fourth Report of the Cancer Assessment Review Committee

PC Code: 069001

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509C)

TO: Linda Taylor, Toxicologist (RRB1)
Christine Olinger, Risk Assessor (RRB1)
Health Effects Division (7509C)

Ann Sibold, PM
Insecticide Branch, Registration Division (7505C)

The Cancer Assessment Review Committee met on December 12, 2007 to evaluate the carcinogenic potential of Pyrethins. Attached please find the Final Cancer Assessment Document.

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

PYRETHRINS (FOURTH REVIEW)

PC Code 069001

FINAL
February 14, 2008

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: _____
Linda Taylor, Toxicologist

DOCUMENT PREPARATION: _____
Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman _____

Karlyn Bailey _____

Lori Brunsman _____

William Burnam, Chair _____

Marion Copley _____

Kit Farwell _____

Ray Kent _____

Mary Manibusan _____

Nancy McCarroll _____

Jess Rowland _____

NON-COMMITTEE MEMBERS IN ATTENDANCE:

John Pletcher, Consulting Pathologist See attached sheet

OTHER ATTENDEES: Ann Sibold (RB/IB), Mike Metzger (HED/RRB1)

TABLE OF CONTENTS

EXECUTIVE SUMMARY

On December 12, 2007, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticides Programs (OPP) met to re-evaluate the hepatocarcinogenic mode of action (MOA) of pyrethrins. This was the fourth evaluation of the cancer classification in light of new mode of action data submitted by the registrant, Pyrethrins Joint Venture (PJV).

Background: The Cancer Peer Review Committee (CPRC) evaluated the carcinogenicity of pyrethrins initially in 1995. The Cancer Assessment Review Committee evaluated the carcinogenicity and mode of action data on two previous occasions, 1999 and 2004.

The CPRC, which met on February 22, 1995 was unable to classify pyrethrins due to questionable accuracy of the histopathology data. The CARC, which met on February 3, 1999, concluded that pyrethrins should be classified as *"Likely to be a Human Carcinogen by the Oral Route"*, based on tumors at two organ sites in Charles River CD rats [liver tumors in females and thyroid tumors in both sexes]. The relevance of the observed tumors to human exposure could not be discounted. The Committee recommended a linear low-dose approach for human risk characterization since there was a lack of data at that time on the mode of action for tumor induction.

The CARC met again on April 14, 2004 to evaluate the available mode of action/mechanistic data on the thyroid and liver tumors in order to determine whether the available data were sufficient to support a change in the carcinogenic classification of pyrethrins, based on the new guidelines. The CARC Committee concluded that the thyroid mode of action data for pyrethrins are consistent with the mode of carcinogenic action that has been established for a number of pesticides that induce thyroid follicular cell tumors in rats and classified pyrethrins as "*Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential"*. With respect to the liver tumors in female rats and the mode of action/mechanistic data available in 2004, the Committee concluded that a causal relationship between enzyme induction and liver tumor formation following pyrethrins exposure had not been established.

Subsequently, the registrant submitted additional information with respect to the liver tumor mode of action, which were considered at the December 12, 2007 CARC meeting. These included (1) three new studies that addressed certain aspects of the proposed mode of action (MOA) for female rat liver tumors (MRIDs 46792703, 46792704, 47036701) and (2) the registrant's weight-of-evidence of the proposed mode of action with respect to the female rat liver tumor response (MRID 47241701 - Mode of Action for Rodent Liver Tumors Produced by Pyrethrins). These data were presented to the CARC on December 12, 2007 by Linda Taylor of the Reregistration Branch I.

The 2007 CARC concluded the following:

Carcinogenicity

Liver Tumors: Administration of pyrethrins was associated with an increase in the incidence of adenomas in female rats at the high dose (3000 ppm). The incidences of liver tumors in females for average daily doses of 0, 100, 1000, and 3000 ppm, respectively were as follows:

Adenomas:	0/58 (0%), 0/25 ((0%), 1/34 (3%), 5/35 (14%)
Carcinomas:	1/42 (2%), 0/20 (0%), 0/28 (0%), 0/32 (0%)
Combined:	1/58 (2%), 0/25 (0%), 1/34 (3%), 5/35 (14%)

Female rats had significant increasing trends and significant differences in the pair-wise comparisons of the 3000 ppm dose group with the controls for hepatocellular adenomas and combined adenomas and/or carcinomas. The incidence at the high dose was in excess of the historical control range of 0-6.0%. The CPRC/CARC considered the liver tumors in female rats to be treatment-related. The dose levels were considered adequate to assess carcinogenicity.

Mode of Action

The overall weight of the evidence supports a non-linear, non-genotoxic, mitogenic mode of action (albeit a weak mitogenic response) for pyrethrins with respect to female rat liver tumors seen at the high dose. This mode of action is relevant to humans (the lack of relevance to humans was not sufficiently demonstrated in the data provided). Furthermore, the data did not support peroxisome proliferation, mutagenesis, or cytotoxicity followed by regenerative proliferation as alternative modes of action.

Classification and Quantification of Carcinogenic Potential

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Pyrethrins as **"Not Likely to be Carcinogenic to Humans" at doses that do not cause a mitogenic response in the liver/cell proliferation**." This is based on a weak liver tumor response seen in female rats only at the high dose. No tumors were seen in male or female mice. The weight of evidence supports a non-genotoxic mitogenic mode of action for liver tumors. The data did not support 1) peroxisome proliferation, 2) mutagenesis or 3) cytotoxicity followed by sustained regenerative proliferation as alternative modes of action for the liver tumor response.

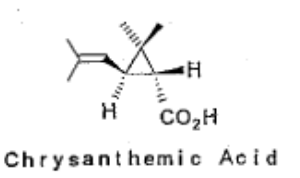
The quantification of carcinogenic potential is not required. The current chronic Reference Dose (cRfD) of 0.04 mg/kg/day is based on the NOAEL of 4.37 mg/kg/day and the traditional 100 Uncertainty Factor (10 for inter-species extrapolation and 10 for intra-species variation). The LOAEL is based on an increased incidence of thyroid follicular cell hyperplasia observed in male rats at 42.9 mg/kg/ day in a chronic toxicity/carcinogenicity study in rats. This RfD would adequately address any chronic effects as well as liver effects induced by pyrethrins at high doses (130 mg/kg/day) in the toxicity/carcinogenicity or mode of action studies in rats.

I. INTRODUCTION

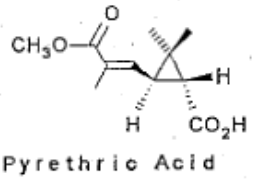
On December 12, 2007, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticides Programs (OPP) met to evaluate the hepatocarcinogenic mode of action (MOA) of pyrethrins. This was a re-evaluation of the cancer classification in light of new mode of action data submitted by the registrant, Pyrethrins Joint Venture (PJV). In addition, the CARC re-evaluated the previously-submitted MOA data and the registrant's weight-of-evidence of the proposed mode of action with respect to the female rat liver tumor response. The new data considered were: additional mode of action studies (MRIDs 46792703, 46792704, 47036701) and a summary document of a series of studies conducted to examine the mode of action by which lifetime administration of pyrethrins results in a slight elevation in liver tumors in the female rat (MRID 47241701).

II. BACKGROUND INFORMATION

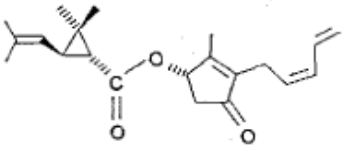
Pyrethrins are natural insecticides produced by certain species of the chrysanthemum plant. There are numerous agricultural, domestic home and garden, pet care, commercial/ industrial/ institutional/food and non-food/mosquito uses of pyrethrins. Pyrethrins are alkaloids. The concentrated extract from these flowers is called pyrethrum. Their relative instability to light limits their use outdoors and on food crops. The structures of the components are shown below.

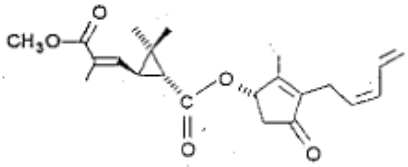


Chrysanthemic Acid



Pyrethric Acid


Pyrethrin I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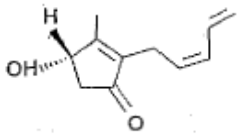
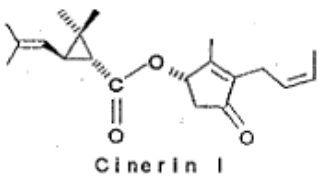
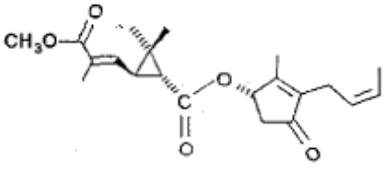
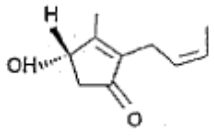


Pyrethrolone

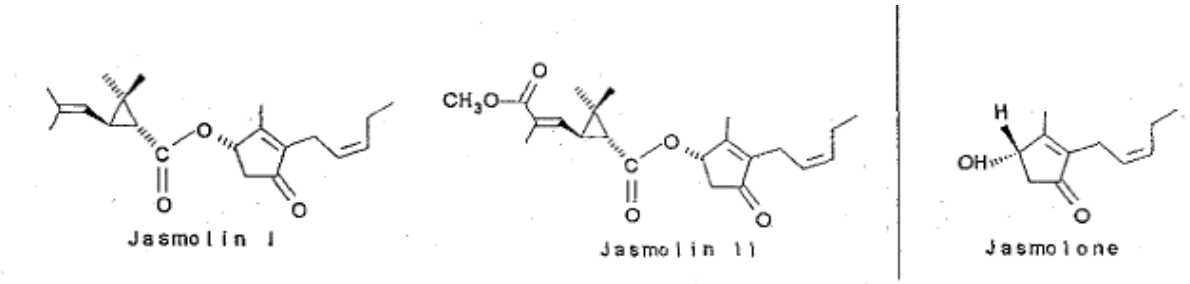

Cinerin I



Cinerin II



Cinerolone



History

First Meeting: The Cancer Peer Review Committee (CPRC) of the Health Effects Division [HED] met on February 22, **1995**, to evaluate the carcinogenic potential of Pyrethrins [TXR No. 0051384]. In the carcinogenicity studies, pyrethrins were administered in the diet to male and female CD-1 mice at 0, 100, 2500, or 5000 ppm for 18 months (equivalent to 0, 13.8, 346 or 686 mg/kg/day in males and 0, 16.6, 413 or 834 mg/kg/day in females, respectively) and to male and female Charles River CD rats at 0 (two separate groups), 100, 1000 or 3000 ppm for 104 weeks (equivalent to 0, 4.37, 42.9 or 130 mg/kg/day for males and 0, 5.39, 55.5 or 173 mg/kg/day for females, respectively). The CPRC concluded that the dose levels tested in CD-1 mice and Charles River CD rats were adequate to assess the carcinogenic potential of pyrethrins.

The Committee was unable to classify pyrethrins for carcinogenicity because of questionable accuracy of the histopathological evaluation for several tissue types. There was sufficient evidence of carcinogenic activity based primarily on thyroid tumors in male and female rats. The Committee, therefore, recommended using the linear low dose extrapolation model for carcinogenic risk assessment, based on combined thyroid follicular cell adenomas and carcinomas in female rats. The Committee also decided to reconsider the classification of pyrethrins for carcinogenicity after reading of additional slides, reevaluation and peer review of pathology data, as well as examination of historical control data and relevant published literature.

Second Meeting: The Cancer Assessment Review Committee (CARC) met on February 3, **1999** to evaluate additional data and the results of pathology peer review submitted by the Pyrethrins Joint Venture (PJV-97), which aided in understanding the carcinogenic response with pyrethrins in the lungs of mice and in the thyroid, liver, parathyroid, skin and ovary of rats [TXR No. 013354]. No mechanistic studies were provided. The CARC concluded that:

Carcinogenicity:

- In CD rats, the occurrence of the thyroid and liver tumors was attributed to the treatment.

  Thyroid: Reevaluation of pathology data indicated a slight difference in the overall count of adenomas (males: 10% and 8% at mid and high, respectively; females: 5% and 8.3% at mid and high dose, respectively). These incidences were outside the historical control range (males: 0%-5%); females: 0%-3.3%).

  The CARC attributed the thyroid tumors to treatment because 1) male and female rats had significant positive trend and significant differences in the pair-wise comparisons for the 1000 ppm (males) and 3000 ppm, for either adenoma and/or combined adenomas and/or

carcinomas, and 2) the incidence of these tumors exceeded the historical control range in both sexes.

Liver: Re-evaluation of liver slides showed an increase in the incidence of adenomas in female rats at the high dose (3000 ppm, 5/60, 8%) compared to none in controls; this incidence (8%) is *in excess* of the historical control range of 0-6.0%. After evaluating the available data, the CARC considered the liver tumors in female rats to be treatment-related.

Female Rat Hepatocellular Tumor Rates[+] and Peto's Prevalence Test Results (p value) - Brunsman (1999)				
	0 ppm	100 ppm	1000 ppm	3000 ppm
Adenomas (%) p =	0/58 (0) 0.000**	0/25 (0) -	1/34 (3) 0.110	5/35 (14) 0.000**
Carcinomas (%)	1/42 (2)	0/20 (0)	0/28 (0)	0/32 (0)
Combined (%) p =	1/58 (2) 0.001**	0/25 (0) -	1/34 (3) 0.386	5/35 (14) 0.005**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
First adenoma observed at week 99.
First carcinoma observed at week 106.
The two control groups were combined for this analysis.
Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level.
If *, then $p<0.05$. If **, then $p<0.01$.

- Parathyroids, skin, ovary: Reanalysis of the pathology data resulted in a determination that the incidence of parathyroid tumors and skin tumors was within the historical control range; and males showed only a significant trend for adenomas (parathyroid). The skin tumors were not considered biologically significant, and reevaluation of the ovary resulted in a classification changed from ovarian theca cell tumors to stromal hyperplasia. The CARC concluded that these tumors were not treatment-related.

- The lung carcinomas in male CD-1 mice were not treatment-related since the incidences at 2500 and 5000 ppm (3/55, 5%, p=0.036 and 3/54, 6%, p=0.034, respectively) were within the historical control range (0%-8%). For female mice there was no evidence for carcinogenic response.

Mutagenicity: Pyrethrins have been tested in each of the three major categories of mutagenicity/ genotoxicity testing of gene mutations, structural chromosomal aberrations and other genotoxic effects. No evidence of positive mutagenicity or genotoxicity was apparent in studies deemed to be acceptable to the Agency.

1999 Cancer Classification: In accordance with the EPA *Proposed Guidelines for Carcinogen Risk Assessment* (April 10, 1996), the Committee classified pyrethrins as **"Likely to be a Human Carcinogen by the Oral Route"** based on the following weight-of-the-evidence considerations:

1. Tumors at two organ sites were seen in Charles River CD rats including liver tumors in females, and thyroid tumors in males and females;

2. The relevance of the observed tumors to human exposure cannot be discounted

3. Since there are no carcinogenicity studies by other routes of exposure, pyrethrins are assumed to be carcinogenic by these other routes.

The Committee recommended a linear low-dose approach for human risk characterization. For the linear low-dose (Q_1*) approach, extrapolation of risk should be based on the most potent Q_1* value of the two tumor types. This extrapolation is supported by the lack of data on the mode of action for tumor induction [TXR No. 013169]. The most potent unit risk, Q_1^* $(mg/kg/day)^{-1}$, of Pyrethrins is 5.14×10^{-3} in human equivalents, based upon **male rat combined (adenomas and/or carcinomas) thyroid follicular cell tumor rates.**

Third Meeting: The Cancer Assessment Review Committee (CARC) met on April 14, **2004** to evaluate the available mode of action/mechanistic data on the thyroid and liver and to determine whether the available data were sufficient to support a change in the carcinogenic classification of pyrethrins, based on the new guidelines [TXR No. 0052631]. The CARC Committee concluded that the thyroid mode of action data for pyrethrins are consistent with the mode of carcinogenic action that has been established for a number of pesticides that induce thyroid follicular cell tumors in rats and classified pyrethrins as "**Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential",** based on the following weight-of-the-evidence considerations:

(i) The occurrence of a benign and minimal liver tumor response only in female Crl:CD® (SD)IGS BR rats.

(ii) There was no treatment-related increase in liver tumors in male Crl:CD®(SD)IGS BR rats.

(iii) There was no treatment-related increase in tumors in either sex of Charles River CD mice.

(iv) There is no concern for mutagenicity.

The Committee further recommended that no quantification of human carcinogenic risk be determined for pyrethrins.

With regard to the thyroid tumors, there was a weak tumor response in a susceptible laboratory animal species that is not of concern for humans. The mode of action data for pyrethrins is consistent with the mode of carcinogenic action that has been established for a number of pesticides that induce thyroid follicular cell tumors in rats (Hurley et al., 1998). This mode of action involves a reduction of circulating thyroid hormone, which activates homeostatic processes that increase thyroid stimulating hormone (TSH) release from the pituitary. TSH release stimulates the thyroid gland to increase thyroid hormone synthesis and release. Persistently elevated TSH levels will lead to thyroid follicular cell hypertrophy and hyperplasia. While these effects are reversible on removal of the TSH stimulus, at least early in the process, continuous stimulation of the thyroid by TSH can lead to neoplasia.

With respect to the liver tumors in female rats and the mode of action/mechanistic data available in 2004, the Committee concluded that a causal relationship between enzyme induction and liver tumor formation following pyrethrins exposure had not been established.

III. MODE OF ACTION ANALYSIS OF PYRETHRINS – LIVER TUMORS

Introduction

The Pyrethrins Joint Venture (PJV) has submitted a mode of action analysis for rodent liver tumors produced by pyrethrins (MRID 47241701). The framework used by the PJV for their analysis is stated to be based on the one developed by the International Life Sciences Institute (ILSI) working group on the relevance of rodent tumors to humans (Cohen, *et al.*, 2003; Meek, *et al.*, 2003; Cohen , *et al.*, 2004). Because of the extensive investigations previously reported in the literature on the MOA of rodent hepatic tumors induced by phenobarbital, the PJV included Phenobarbital as a reference compound in their MOA studies performed on pyrethrins.

Summary description of hypothesized mode of action

The postulated MOA involves activation of the nuclear Constitutive Androstane Receptor (CAR) with a resulting mitogenic effect to include increased cell proliferation and liver hypertrophy. The key events associated with liver tumors produced by phenobarbital-type compounds are as follows (Holsapple, *et al.*, 2006):

- Activation of CAR
- Development of altered hepatic foci
- Increased cell proliferation (as indicated by DNA synthesis)
- Inhibition of apoptosis

Other events that may contribute to the formation of tumors or be secondary to the events listed above, but do not appear to be essential, are as follows:

- Liver hypertrophy
- Disruption of Gap Junctional Intracellular Communication (GJIC)
- Increased oxidative stress

Mitogenic Mode of Action

Mechanistic studies submitted were supportive of the postulated mitogenic mode of action. The CARC concluded that adequate and sufficient evidence were provided for the following key causal events.

A. Data to support the Key Events for a mitogenic mode of action:

1. **Activation of CAR (Induction of CYP P450/CYPs as surrogate for CAR activation)**

Activation of CAR nuclear receptor by pyrethrins was not demonstrated directly. The measurement of CYP2B induction was used as a surrogate for the measurement of CAR.

In the *in vivo* rat study (MRIDs 45889802 and 45889803), CYP-dependent enzyme activities [CYP1A-dependent (7-ethoxyresorufin-O-deethylase), CYP2B-dependent (7-pentoxyresorufin

O-depentylase and testosterone, and CYP3A-dependent (testosterone 6β-hydroxylase)] were increased in both sexes at 8000 ppm and in females at 3000 ppm (tumorigenic dose) following 7, 14, and 42 days (Tables 1 and 2).

In the *in vitro* study (MRID 46792703), pyrethrins induced CYP2B and CYP3A isoforms in both cultured rat and human hepatocytes. There was an induction of 7-benzyloxy-4-trifluoromethylcoumarin O-debenzylase (BFC) activity (a CYP1A/2B isoform marker) and CYP2B1 and CYP2B1/2 mRNA levels in rat hepatocytes and an induction of the CYP3A-dependent testosterone 6β-hydroxylase and CYP3A4 and CYP2B6 mRNA levels in human hepatocytes (Tables 3 and 4).

Increased enzyme induction was demonstrated (MRIDs 45889802, 45889803 and 46792703).

Table 1. Sprague-Dawley *FEMALE* rats (*in vivo* exposure) [MRIDs 45889802 and 45889803]						
KEY EVENTS	**DOSE (PPM)**					
	0	100	1000	3000	8000	PB
7 days exposure						
microsomal protein content (mg/g liver)	27.0±2.8	25.7±3.4		28.6±4.4 (106)	24.8±2.1	28.1±5.3 (104)
cytochrome P450 content (nmol/mg protein)	0.58±0.05	0.54±0.03		0.53±0.06	0.66±0.07** [114]	0.89±0.14*** [153]
7 ethoxyresorufin O-deethylase Nmol/min/mg protein	61±14	47±7		85±20** [139]	81±17* [133]	66±22 [108]
7-pentoxyresorufin O-depentylase nmol/min/mg protein	19±4	21±7		102±36*** [537]	555±162*** [2921]	782±430** [4116]
Testosterone 7α-hydroxylase activity nmol/min/mg protein	1.45±0.29	1.71±0.24* [118]		1.67±0.16 [115]	1.59±0.19 [110]	3.22±0.51*** [222]
Testosterone 16β-hydroxylase nmol/min/mg protein	0.03±0.01	0.03±0.01		0.17±0.07*** [567]	0.68±0.17*** [2267]	0.71±0.28*** [2367]
Testosterone 6β-hydroxylase nmol/min/mg protein	0.07±0.02	0.07±0.02		0.19±0.03*** [271]	0.27±0.07*** [386]	0.240.06*** [343]
BrdU staining increased (centrilobular)	0	0		0	0	7**/15
% cells staining + BrdU	5.88	5.68		16.74*	20.60*	17.23*
liver weight absolute BW as covariate Brain weight as covariate	 11.9±1.3 10.94±0.29 11.84±0.40	 11.4±1.3 10.77±0.29 11.39±0.41		 13.7±0.9*** [115] 13.65±0.27*** [125] 13.81±0.40** [117]	 13.4±2.6** [112] 14.70±0.31*** [134] 13.35±0.40** [113]	 12.8±1.0 [108] 13.12±0.27*** [120] 12.84±0.40 [108]
hypertrophy centrilobular periportal diffuse Total (centrilobular, periportal, diffuse)	 0/15 0/15 0/15 0/15	 0/15 0/15 0/15 0/15		 10***/15 0/15 1/15 11/15	 5*/15 2/15 6*/15 13/15	 14***/15 0/15 0/15 14/15
increased mitosis	0	0		7**/15	8**/15	10***/15
14 days exposure						
microsomal protein content (mg/g liver)	32.3±3.21	28.8±3.19		28.1±5.41	36.9±4.66* [114]	31.3±4.24
cytochrome P450 content (nmol/mg protein)	0.58±0.04	0.57±0.08		0.58±0.05	0.74±0.16** [128]	0.98±0.06*** [169]
7 ethoxyresorufin O-deethylase Nmol/min/mg protein	67±19.5	64±15.8		98±39.6* [146]	122±21.7*** [182]	94±17.6* [140]
7-pentoxyresorufin O-depentylase nmol/min/mg protein	21±11.6	19±3.0		158±43.6*** [752]	831±454*** [3957]	1272±455*** [6057]
testosterone 7α-hydroxylase activity nmol/min/mg protein	1.50±0.16	1.45±0.23		1.47±0.36	1.58±0.20	3.35±0.52*** [223]
testosterone 16β-hydroxylase nmol/min/mg protein	0.03±0.01	0.02±∀0.01		0.24±0.06*** [800]	0.79±0.30*** [2633]	1.13±0.47*** [3767]
testosterone 6β-hydroxylase nmol/min/mg protein	0.05±0.02	0.04±0.02		0.20±0.05*** [400]	0.22±0.04*** [440]	0.24±0.07*** [480]
BrdU staining increased centrilobular	0	0		0	0	7**/15

Table 1. Sprague-Dawley *FEMALE* rats (*in vivo* exposure) [MRIDs 45889802 and 45889803]						
KEY EVENTS	**DOSE (PPM)**					
	0	100	1000	3000	8000	PB
periportal Diffuse	0 0	0 0		0 5*/15	7**/15 0	0 0
% cells staining + BrdU	6.01	5.37		16.77*	19.28*	21.13*
liver weight absolute BW as covariate brain weight as covariate	 12.6±1.8 11.79±0.35 12.51±0.46	 12.1±1.1 11.96±0.33 12.13±0.46		 14.5±1.5** [116] 15.00±0.34*** [127] 14.43±0.46** [115]	 18.9±2.3*** [143] 18.51±0.35*** [157] 17.93±0.47*** [143]	 15.1±2.0*** [120] 14.94±0.33*** [127] 15.17±0.46*** [121]
hypertrophy centrilobular periportal diffuse Total (centrilobular, periportal, diffuse)	 0/15 0/15 0/15 0/15	 0/15 0/15 0/15 0/15		 7**/15 1/15 3/15 11/15	 0/15 2/15 10***/15 12/15	 15***/15 0/15 0/15 15/15
Increased mitosis	0	0		5*/15	3/15	10***/15
42 days exposure						
microsomal protein content (mg/g liver)	27.0±2.57	28.1±6.61		28.3±4.12	35.6±3.95*** [132]	-
cytochrome P450 content (nmol/mg protein)	0.66±0.05	0.72±0.08		0.88±0.14*** [133]	0.84±/13** [127]	-
7 ethoxyresorufin O-deethylase nmol/min/mg protein	 60±7.3	 67±7.3 [112]		 132±47.1** [220]	 104±21.4*** [173]	 -
7-pentoxyresorufin O-depentylase nmol/min/mg protein	 24±2.8	 25±3.2		 229±129.5** [954]	 854±436** [3558]	 -
Testosterone 7α-hydroxylase activity nmol/min/mg protein	 1.71±0.29	 1.88±0.44 [110]		 2.26±0.53* [132]	 1.81±0.34	 -
Testosterone 16β-hydroxylase nmol/min/mg protein	 0.04±0.1	 0.04±0.01		 0.39±0.16*** [975]	 0.89±0.38*** [2225]	 -
Testosterone 6β-hydroxylase nmol/min/mg protein	 0.10±0.02	 0.13±0.03 [130]		 0.26±0.08*** [260]	 0.38±0.09*** [380]	 -
BrdU staining increased centrilobular periportal Diffuse	 0 0 0	 0 0 0		 0 0 0	 0 2/15 2/15	 - - -
% cells staining + BrdU	4.28	5.62		3.71	6.54	-
liver weight absolute BW as covariate brain weight as covariate	 13.4±1.4 13.2±2.7 13.4±0.3	 12.8±1.2 12.4±2.7* 12.8±0.3		 16.1±1.2*** [120] 16.0±2.6*** [122] 16.1±0.3*** [120]	 18.2±1.1*** [135] 19.0±3.1*** [144] 18.17±0.3*** [135]	 - - -
hypertrophy centrilobular periportal diffuse Total (centrilobular, periportal, diffuse)	 0/15 0/15 0/15 0/15	 0/15 0/15 0/15 0/15		 12***/15 1/15 1/15 14/15	 4/15 1/15 7**/15 12/15	 - - -

Table 1. Sprague-Dawley *FEMALE* rats (*in vivo* exposure) [MRIDs 45889802 and 45889803]						
KEY EVENTS	**DOSE (PPM)**					
	0	100	1000	3000	8000	PB
42 days exposure + 42 days recovery						
microsomal protein content (mg/g liver)	33.8±6.13	34.4±8.67		25.3±2.64** [75]	24.5±73*** [73]	-
cytochrome P450 content (nmol/mg protein)	0.59±0.05	0.53±0.06* [90]		0.57±0.05	0.59±0.05	-
7 ethoxyresorufin O-deethylase nmol/min/mg protein	43±8.7	39±11		37±4.7	40±8.6	-
7-pentoxyresorufin O-dependentylase nmol/min/mg protein	21±3	18±3.4		19±2.7	22±3.6	-
testosterone 7α-hydroxylase activity nmol/min/mg protein	1.42±0.18	1.16±0.13		1.43±0.23	1.54±0.07	-
testosterone 16β-hydroxylase nmol/min/mg protein	0.04±0.01	0.03±0.01		0.03±0.01	0.04±0.01	-
testosterone 6β-hydroxylase nmol/min/mg protein	0.11±0.04	0.08±0.03		0.09±0.02	0.09±0.03	-
BrdU staining increased (centrilobular)						
% cells staining + BrdU	2.84	2.72		2.08	0.80	-
liver weight Absolute	13.4±1.5	13.4±1.7		13.9±2.0	13.6±1.5	-
rat bioassay						
liver weight Control 1 absolute relative to body weight relative to brain weight Control 2 absolute relative to body weight relative to brain weight	 17.0±3.0 4.18±1.06 8.25±1.41 19.7±4.2 3.99±0.75 9.76±1.88	 18.3±4.6 3.86±0.67 8.87±2.37	 17.8±4.9 4.09±0.77 8.65±2.36	 18.7±3.5 [110, 95] 4.67±0.82*[a] 9.12±1.76 [111, 93]	N/A	N/A
Hypertrophy	-	-	-	-	N/A	N/A
liver adenomas	0/58	0/25	1/34	5/35**	N/A	N/A

Highlighted column shows data at the dose where liver tumors were increased in females in the rat bioassay
***p <0.05; ** p<0.01; ***p <0.001**
[a]**Relative to Control 2**

Table 2. Sprague-Dawley *MALE* rats (*in vivo* exposure) [MRIDs 45889802 and 45889803]						
KET EVENTS	**DOSE (PPM)**					
	0	100	1000	3000	8000	PB
7 days exposure						
microsomal protein content (mg/g liver)	28.8±4.57				39.8±7.07** [138]*	40.1±4.01*** [139]
cytochrome P450 content (nmol/mg protein)	0.74±0.07				1.19±0.14*** [161]	1.42±0.32*** [192]
7 ethoxyresorufin O-deethylase nmol/min/mg protein	51±9				120±35*** [235]	140±37*** [275]
7-pentoxyresorufin O-dependentylase nmol/min/mg protein	92±33				1036±268*** [1126]	3101±480*** [3371]
testosterone 7α-hydroxylase activity nmol/min/mg protein	0.47±0.09				0.57±0.11 [121]	1.11±0.24*** [236]
testosterone 16β-hydroxylase nmol/min/mg protein	0.05±0.02				0.65±0.14*** [1300]	1.59±0.25*** [3180]
testosterone 6β-hydroxylase nmol/min/mg protein	0.63±0.04				1.05±0.18*** [167]	1.33±0.25*** [211]
BrdU staining increased (centrilobular)	0				0	0
% cells staining + BrdU	2.13				10.19*	25.88*
liver weight absolute body weight as co-variant brain weight as co-variant	 18.8±1.6 18.09±0.43 18.9±0.5				 22.5±2.1*** [119] 23.1±0.4*** [128] 22.3±0.5*** [119]	 23.1±2.2*** [123] 23.2±0.4*** [128] 23.3±0.5*** [124]
hypertrophy centrilobular periportal diffuse Total (centrilobular, periportal, diffuse)	 0/15 0/15 0/15 0/15				 5*/15 1/15 8*/15 14/15	 15***/15 0/15 0/15 15/15
Necrosis	0				0	5*
increased mitosis	0				3	15***
14 days exposure						
microsomal protein content (mg/g liver)	36.3±5.84				43.4±5.38* [120]	46.3±4.39** [128]
cytochrome P450 content (nmol/mg protein)	0.78±0.09				1.07±0.10*** [137]	1.61±0.17*** [206]
7 ethoxyresorufin O-deethylase nmol/min/mg protein	54±12				125±16*** [232]	207±14*** [383]
7-pentoxyresorufin O-dependentylase nmol/min/mg protein	100±37				737±182*** [737]	3160±447*** [3160]
testosterone 7α-hydroxylase activity nmol/min/mg protein	0.46±0.09				0.52±0.06	1.27±0.20*** [276]
testosterone 16β-hydroxylase nmol/min/mg protein	0.06±0.01				0.62±0.14*** [1033]	1.73±0.28*** [2883]
testosterone 6β-hydroxylase nmol/min/mg	0.81±0.24				1.27±0.26*** [157]	2.29±0.10*** [283]

Table 2. Sprague-Dawley *MALE* rats (*in vivo* exposure) [MRIDs 45889802 and 45889803]						
KET EVENTS	**DOSE (PPM)**					
	0	100	1000	3000	8000	PB
protein						
BrdU staining increased (centrilobular) periportal increased	0 0 0				0 4 1	0 0 3
% cells staining + BrdU	2.56				8.26*	2.47
liver weight absolute relative to body weight relative to brain weight	 17.9±2.1 17.66±0.36 17.94±0.61				 25.3±2.1*** [141] 26.43±0.38*** [150] 25.21±0.64*** [141]	 25.5±2.7*** [142] 24.60±0.37*** [139] 25.53±0.62*** [142]
hypertrophy centrilobular periportal diffuse Total (centrilobular, periportal, diffuse)	 0/15 0/15 0/15 0/15				 1/15 3/15 5*/15 9/15	 15***/15 0/15 0/15 15/15
Necrosis	0				0	5*
increased mitosis	0				1	0
42 days exposure						
microsomal protein content (mg/g liver)	32.4±2.64				37.1±2.79** [115]	-
cytochrome P450 content (nmol/mg protein)	0.81±0.08				1.13±0.13*** [140]	-
7 ethoxyresorufin O-deethylase nmol/min/mg protein	83±25				212±39*** [255]	-
7-pentoxyresorufin O-dependentylase nmol/min/mg protein	86±30				667±133*** [776]	-
testosterone 7α-hydroxylase activity nmol/min/mg protein	0.64±0.21				0.52±0.07	-
testosterone 16β-hydroxylase nmol/min/mg protein	0.12±0.04				0.68±0.11*** [567]	-
testosterone 6β-hydroxylase nmol/min/mg protein	1.04±0.21				1.61±0.20*** [155]	-
BrdU staining increased centrilobular periportal	 0 0				 0 3	-
% cells staining + BrdU	1.76				3.39	-
liver weight absolute relative to body weight relative to brain weight	 22.4±3.4 21.66±0.47 22.39±0.74				 30.0±2.4*** [134] 30.73±0.47*** [142] 30.00±0.74 *** [134]	- - -

hypertrophy centrilobular periportal diffuse Total (centrilobular, periportal, diffuse)	 0/15 0/15 0/15 0/15				 2/15 1/15 8**/15 11/15	 - - -
Necrosis	0				0	-
Increased mitosis	0				0	-
42 days exposure + 42 days recovery						
microsomal protein content (mg/g liver)	31.8±1.68				26.9±2.50*** [85]	-
cytochrome P450 content (nmol/mg protein)	0.76±0.06				0.77±0.05	-
7 ethoxyresorufin O-deethylase nmol/min/mg protein	52±10				53±13	-
7-pentoxyresorufin O-depentylase nmol/min/mg protein	76±22				88±23	-
testosterone 7α-hydroxylase activity nmol/min/mg protein	0.51±0.08				0.49±0.08	-
testosterone 16β-hydroxylase nmol/min/mg protein	0.08±0.02				0.09±0.02	-
testosterone 6β-hydroxylase nmol/min/mg protein	0.75±0.14				0.74±0.16	-
BrdU staining increased (centrilobular)	-				-	-
% cells staining + BrdU	-				-	-
liver weight absolute	 21.6±2.0				 23.1±2.3	-
Hypertrophy	-	-	-	-	-	-
rat bioassay						
liver weight Control 1 absolute relative to body weight relative to brain weight Control 2 absolute relative to body weight relative to brain weight	 24.3±4.7 3.83±0.75 10.79±2.12 22.0±4.5 3.64±0.71 9.93±2.04 [92]	 24.7±5.5 4.25±1.07*[a] 11.03±2.59	 24.4±4.5 4.08±0.85 10.90±1.96	 24.9±5.5 4.25±0.72*[a] 11.03±2.48	N/A	N/A
AST (6, 12, 18, 24 months) ALT (6, 12, 18, 24 months)	- -	- -	- -	259%-650%C 561%-3318%C	N/A	N/A
Hypertrophy	-	-	-	-	-	N/A
liver adenomas	6/1	0	3	3	N/A	N/A

*p <0.05; ** p<0.01; ***p <0.001

[a]Relative to Control 2

Table 3. HUMAN HEPATOCYTES (72 hours) MRID 46792703										
µM	0.05	0.2	0.5	2	5	20	50	200	500	1000
Pyrethrins										
MTT Cyto %C	nm	nm	-	-	-	106*	122***	116***	86**	86**
EROD %C	-	-	-	-	-	-	-	-	56**	-
Test 6β OH %C	-	-	-	-	172*	241**	189	64*	36***	35***
CYP3A4 mRNA#	nm	-	-	1.67*	3.24***	8.80***	14.65***	9.11***	6.02***	-
phenobarbital										
MTT Cyto %C	nm	nm	91***	93***	93***	94	-	91***	91***	-
EROD %C	-	-	-	-	-	-	-	-	127	124
Test 6β OH %C	-	-	-	-	-	137	177*	360***	411***	419***
CYP3A4 mRNA#	nm	nm	-	-	-	1.74***	2.94***	7.96***	14.05***	16.25***

MTT assay (measurement of viable mitochondria); nm = not measured; - no significant effect; # compared to 1.00 (control);
*p <0.05; ** p<0.01; ***p <0.001; %C = percent control

Table 4. Female Sprague-Dawley CD RAT HEPATOCYTES (72 hours) MRID 46792703										
µM	0.05	0.2	0.5	2	5	20	50	200	500	1000
Pyrethrins										
MTT Cyto %C	Nm	nm	-	96*	-	-	94**	93***	88***	79***
EROD %C	108**	110***	112***	117***	155***	235***	119***	185***	170***	129***
Test 6β OH %C	-	-	-	-	148*	275***	403***	256***	-	-
BFCOD %C	-	-	-	134***	170***	275***	257***	199***	135***	-
PROD %C	-	-	-	-	125***	135*	-	40***	30***	25***
CYP2B1 mRNA#	1.51	1.50	2.01	1.77**	2.72***	7.55***	4.25***	3.24***	4.25***	5.15***
CYP2B1/2 RNA#	1.21	1.62***	1.63***	2.50***	3.19***	5.08***	4.56***	4.25***	3.71***	4.10***
phenobarbital										
MTT Cyto %C	Nm	nm	-	-	91***	94	-	91***	91***	-
EROD %C	-	92**	93**	89**	-	114**	127***	156***	188***	232***
Test 6β OH %C	-	-	-	-	-	139	137	130	174*	261***
BFCOD %C	-	-	-	-	113**	203***	420***	497***	437***	310***
PROD %C	-	-	-	-	119***	194***	225***	256***	244***	256***
CYP2B1 mRNA#	-	-	-	-	4.37***	9.62***	14.24***	20.95***	16.85***	7.14***
CYP2B1/2 RNA#	-	-	-	1.81*	3.90***	15.41***	20.69***	28.84***	25.74***	17.44***

MTT assay (measurement of viable mitochondria); nm = not measured; - no significant effect; # compared to 1.00 (control);
*p <0.05; ** p<0.01; ***p <0.001; %C = percent control

2. **Development of Altered Hepatic Foci**

A very weak/slight increase (severity only) in basophilic foci was seen in the rat bioassay in females at 3000 ppm. The weak response is consistent with the weak tumor response [PJV Figure 10, page 54 of MRID 47241701].

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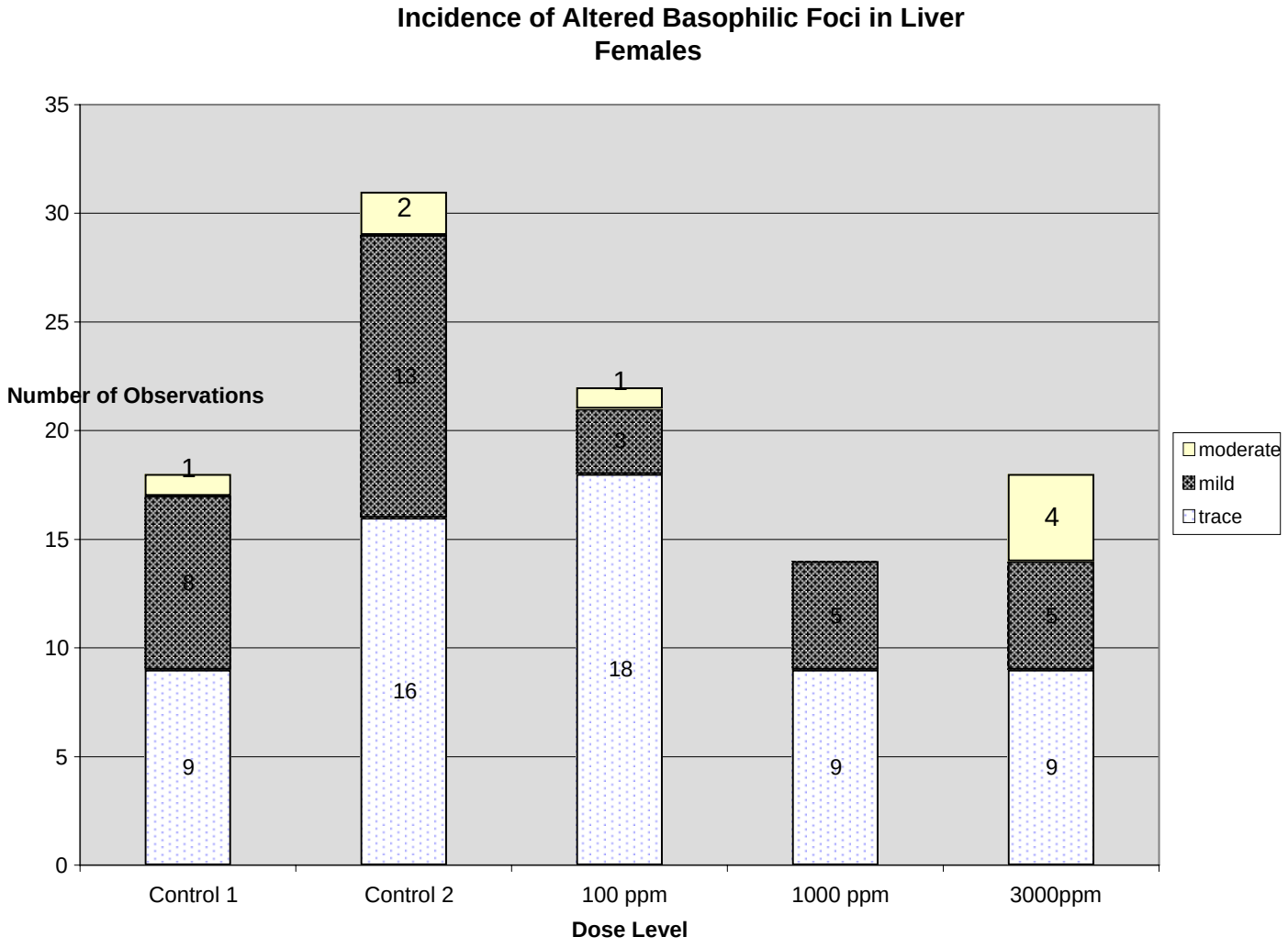

3. **Increased Cell Proliferation (DNA synthesis)**

In the *in vivo* rat study (MRIDs 45889802 and 45889803), the percent of cells staining positive for BrdU was increased in rats of both sexes at 8000 ppm and females at 3000 ppm following 7 and 14 days of exposure but not after 42 days of exposure (Tables 1 and 2 and Figure 11 below).

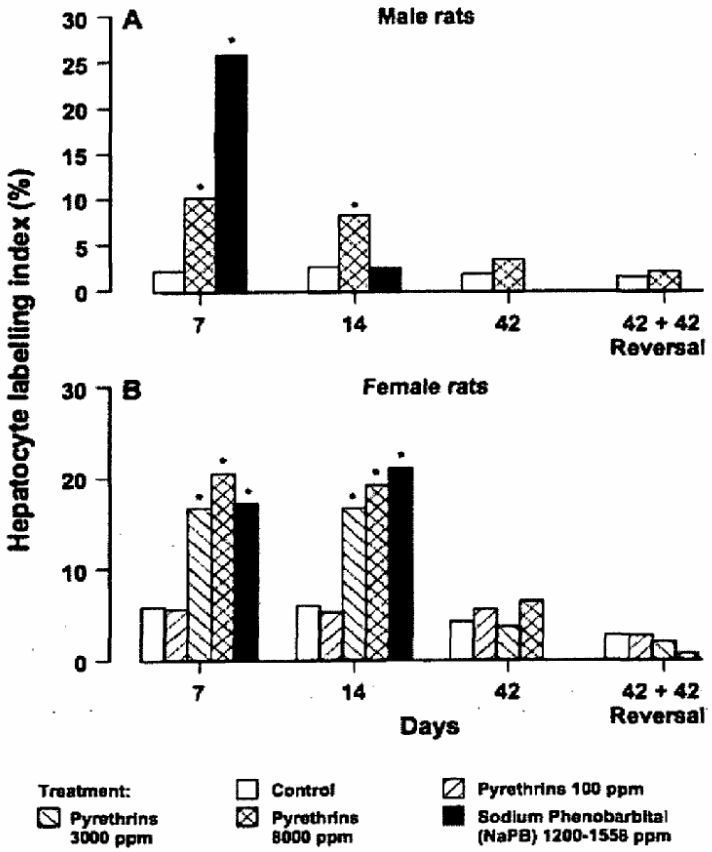

Figure 11:. Effect of treatment of male (A) and female (B) rats with pyrethrins for 7, 14 and 42 days and for 42 days followed by 42 days of reversal, together with PB for 7 and 14 days, on the hepatocyte labelling index. Results are presented as mean values (n=8 rats per group). Values significantly different from controls are: $^{*}p<0.05$.

[Figure 11 is taken from MRID 47241701 using the data from MRID 45889802.]

In the *in vitro* study (MRID 46792704), a significant increase was observed in the labeling index of both male and female rat hepatocytes following 24-hour exposure (Table 5), but no significant increase in labeling index was observed in human hepatocytes following a similar 24-hour exposure.

Table 5. Effect of pyrethrins on F344 rat hepatocyte labeling index (24 hour exposure) MRID 46792704

µg/mL	10	50	100	150	200	250	300	350	400
female	1.1	1.3	1.6*	1.8*	-	-	-	-	-
male	0.9	1.0	1.0	1.1	1.2	1.4	1.3	1.4*	1.5*

fold over control; control = 1.0 (control labeling index + 1.2±0.2); page 34 of MRID 46792704

The increase in BrdU is short-lived (slight burst at 7 and 14 days but not seen at 42 days), which is supportive of a mitogenic response.

4. **Inhibition of Apoptosis**

No conclusion can be reached due to technical problems (both rat and human assessment). The lack of this data does not detract from the MOA argument.

B. Data to support Associative Events:

1. **Liver Hypertrophy/Increased Liver Weights**

Increased liver hypertrophy was observed in the *in vivo* study in females at 3000 ppm (tumorigenic dose) and both sexes at 8000 ppm, following 7, 14, and 42 days exposure (Tables 1 and 2) and in a range-finding (28-day) study at 4000 ppm, 6000 ppm, and 8000 ppm (Table 6). Hypertrophy was not observed in the chronic study at any dose level. Increased liver weights were observed at all dose levels of the 28-day range-finding study (Table 6) and in the *in vivo* study in females at 3000 ppm and both sexes at 8000 ppm following 7, 14, and 42 days exposure (Tables 1 and 2).

Table 6. Sprague-Dawley [Crl:CD®(SD)IGS BR] **Female** Rats (*in vivo* exposure) [MRID 45889801] 28-Day Dose Range-Finding Study

KEY EVENTS	**DOSE (PPM)**			
	0	**4000**	**6000**	**8000**
28 days exposure				
liver weight absolute body weight as covariate brain weight as covariate	 11.37±0.93 10.43±0.31 11.46±0.59	 14.86±1.41*** [131] 15.79±0.31*** [151] 14.84±0.59*** [129]	 16.91±2.22*** [149] 16.66±0.30*** [160] 16.82±0.59*** [147]	 18.01±2.61*** [158] 18.27±0.03*** [175] 18.04±0.59*** [157]
Hypertrophy Diffuse	 0	 4	 8***	 10***
cell proliferation (PCNA slides)	0.99±0.78	1.40±1.98	0.57±0.54	0.55±0.37

n=10

2. **Disruption of Gap Junctional Intracellular Communication (GJIC)**

Slight inhibition of gap junctional intracellular communication was observed in rat hepatocytes (Table 7) following 4- and 24-hour exposures, but no inhibition was observed in human hepatocytes under the conditions of the study (MRID 46792704); however, this non-specific event has minimal relevance to the specific MOA.

Table 7. Cell viability/Gap Junctional Intracellular Communication (GJIC)

µg/mL	50	100	150	200	250	300	350	400	450	500	600	700	800	900	1000	1200
F344 **female rats** (**24** hours)																
MTT %C	98	86	99	41*	45*	32*	29*	40*	27*	19*	-	-	-	-	-	-
GJIC %C	89.8	86.5*	79.6*	-	-	-	-	-	-	-	-	-	-	-	-	-
F344 **female rats** (**4** hours)																
MTT %C	-	100	-	100	-	100	-	100	-	100	100	98	86*	81*	77*	-
GJIC %C	85.2*	84.6*	-	-	78.1*	-	-	72.0*	-	-	-	-	-	-	-	-
F344 **male rats** (**24** hours)																
MTT %C	-	94	-	90	-	97	-	96	-	56*	-	-	-	-	-	-
GJIC %C	97.1	100.9	95.2	-	94.0	-	-	85.0*	-	-	-	-	-	-	-	-
F344 **male rats** (**4** hours)																
MTT %C	-	-	-	-	-	-	-	89	-	95	100	94	100	-	97	74*
GJIC %C	93.3	91.2*	-	-	83.5*	-	-	76.2*	-	-	-	-	-	-	-	-
humans (**24** hours)																
MTT %C	100	100	93	90	98	64*	25*	32*	33*	28*	-	-	-	-	-	-
GJIC %C	-	100.8	98.1	100.1	-	-	-	-	-	-	-	-	-	-	-	-
humans (**4** hours)																
MTT %C	-	100	-	100	-	100	-	98	-	100	82*	50*	68*	53*	63*	-
GJIC %C	-	100.9	99.1	98.2	101.5	-	-	-	-	-	-	-	-	-	-	-

MTT – assay for measurement of cytolethality; %C percent of control; * $p<0.05$

3. **Increased oxidative stress**

There was no evidence of oxidative stress (MRID 46792704); however, it is noted that pyrethrins contain BHT, an antioxidant. Additionally, the assessment was performed in male rats only where there was no increase in liver tumors.

C. Data on Alternative MOAs for Liver Tumors:

1. **Cytotoxicity**

Slight cytotoxicity was observed in rat hepatocytes *in vitro* following a 72-hour exposure period at 5, 200, 500 and 1000 µM pyrethrins (MRID 46792703, Table 4), whereas severe cytotoxicity was observed following 24-hour (at 200-500 µg/mL) and 4-hour (at 800, 900, and 1000 µg/mL) exposure periods (MRID 46792704, Table 7). All of the *in vitro* MOA studies were performed at dose levels below those producing cytotoxicity. In the bioassay, liver cytotoxicity was not

observed in the female rat, but male rats demonstrated significant increases in aspartate aminotransferase (259%-650% of control) and alanine aminotransferase (561%-3318% of control) throughout the study (at 6, 12, 18, and 24 months). Significant increases in AST and ALT were not observed in males at 8000 ppm or in females at 100-8000 ppm following 7, 14, and 42 days of exposure. The chronic toxicity/carcinogenicity study showed evidence of liver toxicity in males only. At the high dose (3000 ppm), there was a significant increase, compared to controls, in aspartate aminotransferase and alanine amino transferase throughout the study in males. However, no liver tumors were seen in males. There was no evidence of cytotoxity in female rats at doses up to and including 3000 ppm. Thus, cytotoxicity is not a likely MOA for formation of liver tumors.

2. **Activation of Peroxisome Proliferator Activated Receptor-alpha (PPARα)**

Peroxisomal proliferation was not shown to be a key event. Although hepatic palmitoyl-CoA oxidation activity was induced in both sexes at 8000 ppm and in females at 3000 ppm, the response was minimal (2-3-fold), and PPARα as a MOA can be ruled out (Table 8).

Table 8. Hepatic whole homogenate protein content and palmitoyl-CoA oxidation activity (MRID 47036701)

Treatment	Protein content (mg protein/g liver)	Palmitoyl-CoA oxidation	
		nmol/min/mg homogenate protein	µmol/min/g liver
MALES			
Control	179±11.4	3.4±0.39	0.62±0.069
8000 ppm	180±3.9	12.3±1.67*** (362)	2.21±0.293*** (357)
FEMALES			
Control	180±5.9	4.1±0.51	0.74±0.087
100 ppm	172±5.3* (96)	3.7±0.54 (90)	0.64±0.102* (87)
3000 ppm	178±3.2	8.5±1.77*** (207)	1.51±0.308*** (204)
8000 ppm	1.80±13.1	12.8±1.60*** (312)	2.30±0.242*** (311)

(% of control); * $p<0.05$; *** $p<0.001$

OVERALL CONCLUSION

The overall weight of the evidence supports a non-linear, non-genotoxic, mitogenic mode of action (albeit a weak mitogenic response) for pyrethrins with respect to female rat liver tumors seen at the high dose (3000 ppm). This mode of action is relevant to humans (the lack of relevance to humans was not sufficiently demonstrated in the data provided). Furthermore, the data did not support peroxisome proliferation, mutagenesis, or cytotoxicity followed by regenerative proliferation as alternative modes of action.

IV. WEIGHT OF THE EVIDENCE CONSIDERATIONS

1. Carcinogenicity

Liver Tumors

Administration of pyrethrins was associated with an increase in the incidence of adenomas in female rats at the high dose (3000 ppm). The incidences of liver tumors in females for average daily doses of 0, 100, 1000, and 3000 ppm, respectively were as follows:

Adenomas:	0/58 (0%), 0/25 ((0%), 1/34 (3%), 5/35 (14%)
Carcinomas:	1/42 (2%), 0/20 (0%), 0/28 (0%), 0/32 (0%)
Combined:	1/58 (2%), 0/25 (0%), 1/34 (3%), 5/35 (14%)

Female rats had significant increasing trends and significant differences in the pair-wise comparisons of the 3000 ppm dose group with the controls for hepatocellular adenomas and combined adenomas and/or carcinomas. The incidence at the high dose was *in excess* of the historical control range of 0-6.0%. The CARC considered the liver tumors in female rats to be treatment-related. The dose levels were considered adequate to assess carcinogenicity.

2. Mode of Action

The overall weight of the evidence supports a non-linear, non-genotoxic, mitogenic mode of action (albeit a weak mitogenic response) for pyrethrins with respect to female rat liver tumors seen at the high dose. This mode of action is relevant to humans (the lack of relevance to humans was not sufficiently demonstrated in the data provided). Furthermore, the data did not support peroxisome proliferation, mutagenesis, or cytotoxicity followed by regenerative proliferation as alternative modes of action.

V. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified Pyrethrins as **"Not Likely to be Carcinogenic to Humans" at doses that do not cause a mitogenic response in the liver/cell proliferation**." This is based on a weak liver tumor response seen in female rats only at the high dose. No tumors were seen in male or female mice. The weight of evidence supports a non-genotoxic mitogenic mode of action for liver tumors. The data did not support 1) peroxisome proliferation, 2) mutagenesis or 3) cytotoxicity followed by sustained regenerative proliferation as alternative modes of action for the liver tumor response.

VI. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The quantification of carcinogenic potential is not required. The current chronic Reference Dose (cRfD) of 0.04 mg/kg/day is based on the NOAEL of 4.37 mg/kg/day and the traditional 100 Uncertainty Factor (10 for inter-species extrapolation and 10 for intra-species variation). The LOAEL is based on an increased incidence of thyroid follicular cell hyperplasia observed in male rats at 42.9 mg/kg/ day in a chronic toxicity/carcinogenicity study in rats. This RfD would adequately address any chronic effects as well as liver effects induced by pyrethrins at high doses (130 mg/kg/day) in the toxicity/carcinogenicity or mode of action studies in rats.

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