

US EPA ARCHIVE DOCUMENT

Image
14



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

TXR No. 0050482

MEMORANDUM

February 21, 2002

SUBJECT: Iprovalicarb Revised Qualitative Risk Assessment Based
on
Hsd/WIN: WU(SPF) Rat Dietary Study

P.C. Code 098359

TO: Ed Budd, Toxicologist
Registration Action Branch 2
Health Effects Division (7509C)

FROM: Virginia Fornillo, Program Analyst *Virginia Fornillo 2/24/02*
Science Information Management Branch
Health Effects Division (7509C)

THROUGH: Jess Rowland, Branch Chief *Jess Rowland 2/25/02*
Science Information Management Branch
Health Effects Division (7509C)

Introduction

An initial Qualitative Risk Assessment Based on Hsd/WIN: WU(SPF) Rat Dietary Study of Iprovalicarb, dated November 6, 2001 (TXR No. 0050257) was made by L. Brunsman. This memorandum includes results of that previous analysis and that of two additional types of tumors which occurred in female rats: uterine mixed muellerian tumors and urinary bladder transitional cell papilloma tumors.

Background

A combined chronic/carcinogenicity study in Hsd/WIN:WU(SPF) rats was conducted by Bayer AG, Wuppertal, Germany, for Bayer Corporation, and issued February 4, 1998 (Report No. 27160; MRID No. 448657-23).

The study design allocated groups of 50 rats per sex to dose levels of 0, 500, 5000, or 20000 ppm (0, 26.0, 262.5, or 1109.6 mg/kg/day for males; 0, 31.7, 326.3, or 1379.7 mg/kg/day for females) of Iprovalicarb for 106 weeks. An additional 10 rats per sex per dose were designated for interim sacrifice at week 53.

Survival Analyses

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of Iprovalicarb in male rats. There were no statistically significant incremental changes in mortality with increasing doses of Iprovalicarb in female rats. See Tables 1 and 2 for mortality test results.

The statistical evaluation of mortality was based upon the Trend and Homogeneity Analyses of Proportions and Life Table Data. (Thomas, Breslow and Gart).

Tumor Analyses

Male rats had significant increasing trends in bone (femur) osteosarcomas, bone (lower jaw) osteosarcomas, and nasal cavity chondrosarcomas, all at $p < 0.05$. Male rats also had a significant increasing trend in bone (femur) osteosarcomas and/or bone (lower jaw) osteosarcomas combined at $p < 0.01$. There was a significant difference in the pair-wise comparison of the 20000 ppm dose group with the control for bone (femur) osteosarcomas and/or bone (lower jaw) osteosarcomas combined at $p < 0.05$.

Female rats had a significant increasing trend in thyroid gland follicular cell adenomas and/or carcinomas combined at $p < 0.05$. There were no significant trends found in either the uterine mixed muellerian or the urinary bladder transitional cell papilloma tumors. In no case were there significant differences in the pair-wise comparisons of the dosed groups with the controls.

The statistical analyses of the male rats were based upon Peto's prevalence test. The statistical analyses of the female rats were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 3 through 7 for the tumor analyses results.

Table 1. Iprovalicarb - Hsd/WIN:WU(SPF) Rat Study
Male Mortality Rates[†] and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	53 ⁱ	53-78	79-107 ^f	
0	0/60	1/60	10/59	5/49	14/44	20/50 (40)*
500	0/60	0/60	10/60	3/50	17/47	20/50 (40)
5000	0/60	3/60	8/57	1/49	13/48	17/52 (33)
20000	0/60	0/60	10/60	3/50	9/47	12/50 (24)

[†]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

ⁱInterim sacrifice at week 53.

^fFinal sacrifice at week 106.

() Percent.

Note: Time intervals were selected for display purposes only.

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. Iprovalicarb - Hsd/WIN:WU(SPF) Rat Study
Female Mortality Rates[†] and Cox or Generalized K/W Test Results

Dose (ppm)	<u>Weeks</u>					Total
	1-26	27-52	53 [‡]	53-78	79-107 [§]	
0	0/60	1/60	10/59	0/49	16/49	17/50 (34)
500	0/60	2/60	9/58	5/49	14/44	21/51 (41)
5000	0/60	0/60	10/60	6/50	10/44	16/50 (32)
20000	0/60	1/60	10/59	4/49	12/45	17/50 (34)

[†]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[‡]Interim sacrifice at week 53.

[§]Final sacrifice at week 106.

() Percent.

Note: Time intervals were selected for display purposes only.

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. Iprovalicarb - Hsd/WIN:WU(SPF) Rat Study

Male Bone Tumor Rates[†] and
Peto's Prevalence Test Results (p values)

	<u>Dose (ppm)</u>			
	0	500	5000	20000
Osteosarcomas (Femur)	0/41	0/39	0/44	2 ^a /47
(%)	(0)	(0)	(0)	(4)
p =	0.0319*	-	-	0.0868
Osteosarcomas (Lower Jaw)	0/59	0/60	0/56	1 ^b /60
(%)	(0)	(0)	(0)	(2)
p =	0.0436*	-	-	0.0984
Combined	0/59	0/60	0/56	3/60
(%)	(0)	(0)	(0)	(5)
p =	0.0003**	-	-	0.0127*

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

^aFirst osteosarcoma (femur) observed at week 89, dose 20000 ppm.

^bFirst osteosarcoma (lower jaw) observed at week 53 not in an interim sacrifice animal, dose 20000 ppm.

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 $p < 0.01$.

Table 4. Iprovalicarb - Hsd/WIN:WU(SPF) Rat Study

Male Nasal Cavity Tumor Rates[†] and
Peto's Prevalence Test Results (p values)

		<u>Dose (ppm)</u>			
		0	500	5000	20000
Chondro- sarcomas (%)	0/35 (0)	0/37 (0)	0/41 (0)	1 ^a /41 (2)	

p = 0.0390*

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before observation of the first tumor.

^aFirst chondrosarcoma observed at week 101, dose 20000 ppm.

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 $p < 0.01$.

6

Table 5. Iprovalicarb - Hsd/WIN:WU(SPF) Rat Study

Female Thyroid Gland Follicular Cell Tumor Rates[†] and
Exact Trend Test and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>			
	0	500	5000	20000
Adenomas (%)	0/49 (0)	0/49 (0)	1/48 (2)	2 ^a /48 (4)
p =	0.0596	1.0000	0.4948	0.2423
Carcinomas (%)	0/49 (0)	0/49 (0)	1 ^b /48 (2)	1/48 (2)
p =	0.1833	1.0000	0.4948	0.4948
Combined (%)	0/49 (0)	0/49 (0)	2/48 (4)	3/48 (6)
p =	0.0228*	1.0000	0.2423	0.1173

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 54. Also excludes week 53 interim sacrifice.

^aFirst adenoma observed at week 82, dose 20000 ppm.

^bFirst carcinoma observed at week 106, dose 5000 ppm.

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 $p < 0.01$.

Table 6. Iprovalicarb - Hsd/WIN:WU(SPF) Rat Study

Female Uterine Mixed Muellierian Tumor Rates[†] and
Exact Trend Test and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>			
	0	500	5000	20000
Mixed Muellierian				
(%)	0/49 (0)	0/49 (0)	1/48 (2)	2 [*] /48 (4)
p =	0.0596	1.0000	0.4948	0.2423

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 54. Also excludes week 53 interim sacrifice.

^{*}First mixed muellierian observed at week 104, dose 20000 ppm.

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 $p < 0.01$.

Table 7. Iprovalicarb - Hsd/WIN:WU(SPF) Rat Study

Female Urinary Bladder Transitional Cell Papilloma Tumor Rates[†] and Exact Trend Test and Fisher's Exact Test Results (p values)

	<u>Dose (ppm)</u>			
	0	500	5000	20000
Papilloma	0/49	0/48	0/48	2 [*] /48
(%)	(0)	(0)	(0)	(4)
p =	0.0609	1.0000	1.000	0.2423

[†]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 54. Also excludes week 53 interim sacrifice.

^{*}First papilloma observed at week 107, dose 20000 ppm.

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 $p < 0.01$.

References

- Cox, D.R. (1972) Regression Models and Life Tables (with discussion). J. Royal Stat. Soc. Ser. B. 34, 187-220.
- Gart, J.J., D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf (1986) The Design and Analysis of Long-Term Animal Experiments. In: Statistical Methods in Cancer Research, Volume III. IARC Scientific Publications No. 79. Lyon, France: International Agency for Research on Cancer, p. 18.
- Peto, R., M. Pike, N. Day, R. Gray, P. Lee, S. Parish, J. Peto, S. Richard, and J. Wahrendorf (1980) Guidelines for Simple, Sensitive, Significant Tests for Carcinogenic Effects in Long-Term Animal Experiments. In: Monographs on the long-term and short-term screening assays for carcinogens: a critical appraisal. IARC Monographs, Supplement 2. Lyon, France: International Agency for Research on Cancer, pp. 311-426.
- Thomas, D.G., N. Breslow, and J.J. Gart (1977) Trend and Homogeneity Analyses of Proportions and Life Table Data. Computers and Biomedical Research 10, 373-381.

10