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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Fluazinam Qualitative Risk Assessment Based On Sprague-Dawley Rat and CD-1 Mouse Dietary Studies

P.C. Code 129098

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Background

A combined chronic toxicity and oncogenicity study in Sprague-Dawley rats was conducted by Huntingdon Research Centre, Ltd., Cambridgeshire, England, for Ishihara Sangyo Kaisha, Ltd., Tokyo, Japan, and dated August 25, 1988 (Report No. ISK 8/87263; MRID No. 42248620).

The study design allocated groups of 50 rats per sex to dose levels of 0, 1, 10, 100 or 1000 ppm of Fluazinam for 104 weeks. An additional 10 rats per sex per dose were designated for interim sacrifice at week 52.

An oncogenicity study in CD-1 mice was conducted by Huntingdon Research Centre, Ltd., Cambridgeshire, England, for Ishihara Sangyo Kaisha, td., Tokyo, Japan, and dated September 29, 1988 (Report No. ISK 9/87264; MRID No. 42208405).

The study design allocated groups of 52 mice per sex to dose levels of 0, 0, 1, 10, 100 or 1000 ppm of Fluazinam for 104 weeks. The two concurrent control groups have been combined for the purposes of these analyses.

An oncogenicity study in CD-1 mice was conducted by Huntingdon Life Sciences, Ltd., Cambridgeshire, England, for Ishihara Sangyo Kaisha, Ltd., Tokyo, Japan, and dated December 19, 1996 (Report No. ISK 50/950671; MRID No. 44807222). In May of 1998, with the consensus of the sponsor and Huntingdon Life Sciences, the microscopic findings for 3 male mice were revised. In May of 2000, at the request of the EPA, a Pathology Working Group (PWG) was convened to peer review the liver slides of the male mice. The results of the PWG have been used for these analyses.

The study design allocated groups of 50 mice per sex to dose levels of 0, 1000, 3000 or 7000 ppm of Fluazinam for 104 weeks to males and 97 weeks for females. An additional twenty animals per sex were added to the control and high dose groups and necropsied after treatment for 78 weeks.

Survival Analyses

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Fluazinam in male or female rats, male mice of either study, or female mice of the 1988 study. Female mice of the 1996 study showed an increasing trend for mortality with increasing doses of Fluazinam. See Tables 1 and 2 for rat mortality test results, Tables 4 and 5 for the 1988 mouse study mortality test results, and Tables 7 and 8 for the 1996 mouse study mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had significant increasing trends in thyroid gland follicular cell carcinomas and adenomas and/or carcinomas combined, both at $p < 0.05$. There was a significant difference in the pair-

wise comparison of the 1000 ppm dose group with the controls for thyroid gland follicular cell adenomas and/or carcinomas combined at $p < 0.05$.

There were no compound-related tumors observed in female rats.

Male mice of the 1988 study had significant increasing trends, and significant differences in the pair-wise comparisons of the 1000 ppm dose group with the controls, for hepatocellular adenomas and adenomas and/or carcinomas combined, at $p < 0.05$ for the adenomas, and at $p < 0.01$ for the combined. There was also a significant trend in hepatocellular carcinomas at $p < 0.01$, and a significant difference in the pair-wise comparison of the 1000 ppm dose group with the controls for hepatocellular carcinomas at $p < 0.05$.

There were no compound-related tumors observed in female mice of the 1988 study.

Male mice of the 1996 study (based on the 2000 PWG consensus) showed no significant increasing trends. There were significant differences in the pair-wise comparisons of the 3000 ppm dose group with the controls for hepatocellular adenomas and adenomas and/or carcinomas combined, both at $p < 0.01$. There was also a significant difference in the pair-wise comparison of the 7000 ppm dose group with the controls for hepatocellular adenomas and/or carcinomas combined at $p < 0.05$.

Female mice of the 1996 study had a significant increasing trend in hepatocellular adenomas and/or carcinomas combined at $p < 0.01$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

The statistical analyses of the rats, the 1988 mouse study (both sexes) and the male mice of the 1996 study (2000 PWG consensus) were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Table 3 for rat tumor analysis results. See Table 6 for the 1988 mouse study tumor analysis results. See Tables 9 and 10 for the 1996 mouse study tumor analysis results.

Table 1. Fluazinam - Sprague-Dawley Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	52[i]	53-78	79-106[f]	Total
0	1/60	1/59	10/58	7/48	27/41	36/50 (72)
1	0/60	1/60	10/59	9/49	22/40	32/50 (64)
10	1/60	1/59	10/58	7/48	25/41	34/50 (68)
100	0/60	3/60	8/57	4/49	23/45	30/52 (58)
1000	0/60	4/60	9/56	13/47	12/34	29/51 (57)

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

[i]Interim sacrifice at week 52.
[f]Final sacrifice at week 104.

( )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. Fluazinam - Sprague-Dawley Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	52[i]	53-78	79-106[f]	Total
0	1/60	0/59	10/59	10/49	21/39	32/50 (64)
1	0/60	0/60	10/60	5/50	20/45	25/50 (50)
10	1/60	0/59	10/59	4/49	21/45	26/50 (52)
100	0/59[a]	0/59	10/59	4/49	24/45	28/49 (57)
1000	0/60	1/60	10/59	5/49	14/44	20/51 (40)*

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

[i]Interim sacrifice at week 52.
[f]Final sacrifice at week 104.
[a]One accidental death at week 13, dose 100 ppm.

( )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. Fluazinam - Sprague-Dawley Rat Study

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

	Dose (ppm)				
	0	1	10	100	1000
Adenomas (%)	4/48 (8)	3/34 (9)	5/38 (13)	5[a]/34 (15)	8/47 (17)
p =	0.113	0.618	0.353	0.288	0.167
Carcinomas (%)	0/48 (0)	0/34 (0)	0/38 (0)	1/34 (3)	3[b]/47 (6)
p=	0.011*	1.000	1.000	0.415	0.117
Combined (%)	4/48 (8)	3/34 (9)	5/38 (13)	6/34 (18)	11/47 (23)
p =	0.018*	0.618	0.353	0.177	0.041*

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[a]First adenoma observed at week 70, dose 100 ppm.

[b]First carcinoma observed at week 68, dose 1000 ppm.

Note: Interim sacrifice animals are not included in this analysis. There were no thyroid gland follicular cell tumors in any interim sacrifice animals.

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. Fluazinam - 1988 CD-1 Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53-78	79-105[f]	Total
0	1/103[a]	6/100[b]	22/94	32/72	61/101 (60)
1	2/52	2/50	8/48	22/39[c]	34/51 (67)
10	1/52	2/50[d]	11/48	14/37	28/51 (55)
100	4/52	7/48	7/41	14/34	32/52 (62)
1000	1/52	1/51	4/50	23/46	29/52 (56)

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

[f]Final sacrifice at week 104.

[a]One accidental death at week 6, dose 0 ppm.
[b]Two accidental deaths, one each at weeks 42 and 52, dose 0 ppm.
[c]One accidental death at week 104, dose 1 ppm.
[d]One accidental death at week 52, dose 10 ppm.

( )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 5. Fluazinam - 1988 CD-1 Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53-78	79-106[f]	Total
0	1/104	2/103	7/101	33/94	43/104 (41)
1	1/52	2/51	3/49	15/46	21/52 (40)
10	0/52	0/52	3/52	16/49	19/52 (37)
100	0/52	1/52	1/51	17/50	19/52 (37)
1000	0/52	2/52	3/49[a]	19/46	24/51 (47)

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

[f]Final sacrifice at week 104.

[a]One accidental death at week 56, dose 1000 ppm.

( )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 6. Fluazinam - 1988 CD-1 Mouse Study

Male Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)				
	0	1	10	100	1000
Adenomas (%)	15/94 (16)	12/48 (25)	9/48 (19)	7/41 (17)	17[a]/50 (34)
p =	0.012*	0.142	0.421	0.527	0.013*
Carcinomas (%)	18/94 (19)	8/48 (17)	7/48 (15)	7/41 (17)	17[b]/50 (34)
p=	0.006**	0.454	0.334	0.490	0.039*
Combined (%)	31[c]/94 (33)	18[c]/48 (38)	15[d]/48 (31)	12[c]/41 (29)	31[e]/50 (62)
p =	0.000**	0.361	0.496	0.415	0.001**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[a]First adenoma observed at week 56, dose 1000 ppm.

[b]First carcinoma observed at week 56, dose 1000 ppm.

[c]Two animals in each of the control, 1 and 100 ppm dose groups had both an adenoma and a carcinoma.

[d]One animal in the 10 ppm dose group had both an adenoma and a carcinoma.

[e]Three animals in the 1000 ppm dose group had both an adenoma and a carcinoma.

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. Fluazinam - 1996 CD-1 Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (ppm)	Weeks 1-26	27-52	53-78	79[i]	79-105[f]	Total
0	1/70	3/69	15/66	14/51	19/37	38/56 (68)
1000	0/50	2/50	10/48	0/38	12/38	24/50 (48)
3000	2/50	1/48	6/47	0/41	19/41	28/50 (56)
7000	2/70	4/68	8/64	16/56	25/40	39/54 (72)

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

[i]Interim sacrifice at week 79.

[f]Final sacrifice at week 104.

( )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 8. Fluazinam - 1996 CD-1 Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	53-78	79[i]	79-98[f]	Total
0	1/68[a]	2/67	14/65	12/51	10/39	27/56 (48)*
1000	1/50	3/49	13/46	0/33	7/33	24/50 (48)
3000	0/50	2/50	15/48	0/33	6/33	23/50 (46)
7000	0/68[a]	1/68	22/67	13/45	19/32	42/55 (76)**

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

[i]Interim sacrifice at week 79.
[f]Final sacrifice at week 97.

[a]Two animals in each of the control and 7000 ppm dose groups were missexed at study initiation and subsequently removed from the study.

( )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 9. Fluazinam - 1996 CD-1 Mouse Study

2000 PWG Consensus

Male Hepatocellular Tumor Rates+ and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (ppm)			
	0	1000	3000	7000
Adenomas (%)	11[a]/66 (17)	13/48 (27)	22/47 (47)	19/64 (30)
p =	0.078	0.133	0.001**	0.060
Carcinomas (%)	1/66 (2)	2[b]/48 (4)	4/47 (9)	5/64 (8)
p=	0.069	0.382	0.095	0.097
Combined (%)	12/66 (18)	15/48 (31)	23[c]/47 (49)	21[c]/64 (33)
p =	0.069	0.082	0.001**	0.043*

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

[a]First adenoma observed at week 71, dose 0 ppm.

[b]First carcinoma observed at week 79, dose 1000 ppm.

[c]Three animals in each of the 3000 and 7000 ppm dose groups had both an adenoma and a carcinoma.

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 10. Fluazinam - 1996 CD-1 Mouse Study

Female Hepatocellular Tumor Rates[+] and
Peto's Prevalence Test Results (p values)

	Dose (ppm)			
	0	1000	3000	7000
Adenomas (%)	1/52 (2)	0/33 (0)	3/37 (8)	3[a]/46 (7)
p =	0.053	-	0.128	0.055
Carcinomas (%)	0/29 (0)	0/26 (0)	1[b]/27 (4)	0/13 (0)
p=	0.344	-	0.150	-
Combined (%)	1/52 (2)	0/33 (0)	4/37 (11)	3/46 (7)
p =	0.048*	-	0.068	0.055

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

[a]First adenoma observed at week 76, dose 7000 ppm.

[b]First carcinoma observed at week 97, dose 3000 ppm, in a final sacrifice animal.

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 $p < 0.01$.

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