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MEMORANDUM

SUBJECT: Metam Sodium Qualitative Risk Assessment Based On Hsd/Ola: Wistar Tox Rat and C57BL/10JfCD-1/Alpk Mouse Drinking Studies

Caswell No. 780

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Summary

This qualitative risk assessment of Metam Sodium was based upon two chronic drinking studies conducted in Hsd/Ola: Wistar Tox rats and C57BL/10JfCD-1/Alpk mice. The rats received 0, 0.019, 0.056, or 0.19 mg/ml of Metam Sodium in drinking water (0, 1.3, 3.9, or 12.0 mg/kg/day for males; 0, 2.3, 6.2, or 16.2 mg/kg/day for females) for 105 weeks. The mice received 0, 0.019, 0.074, or 0.23 mg/ml of Metam Sodium in drinking water (0, 1.6, 6.5, or 27.7 mg/kg/day for males; 0, 2.3, 8.7, or 29.9 mg/kg/day for females) for 105 weeks.

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of Metam Sodium in male rats. Female rats showed no significant incremental

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changes in mortality with increasing doses of Metam Sodium.

There were no statistically significant increasing trends in the tumor rates of male rats. However, there were significant differences in the pair-wise comparisons of the 1.3 and 3.9 mg/kg/day dose groups with the controls for hemangiosarcomas.

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

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Metam Sodium in male or female mice.

Male mice had significant dose-related increasing trends in liver, spleen, bone marrow (femur), bone marrow (spine), and subcutaneous tissue angiosarcomas, angiosarcomas at all other sites, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined. There was a significant difference in the pair-wise comparison of the 1.6 mg/kg/day dose group with the controls for liver angiosarcomas. There were significant differences in the pair-wise comparisons of the 27.7 mg/kg/day dose group with the controls for liver, spleen, and bone marrow (femur) angiosarcomas, angiosarcomas at all other sites, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined.

Female mice had significant dose-related increasing trends in liver angiosarcomas, spleen angiosarcomas, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined. There were significant differences in the pair-wise comparisons of the 8.7 and 29.9 mg/kg/day dose groups with the controls for spleen angiosarcomas.

Background

A chronic toxicity and carcinogenicity study in Harlan Olac Limited Shaws Farm Hsd/Ola: Wistar Tox rats was conducted by Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, United Kingdom, for the Metam Sodium Task Force, and dated May 23, 1994 (Report No. CTL/P/4139; Study No. PR0838; MRID No. 432758-02).

The study design allocated groups of 52 rats per sex to dose

levels of 0, 0.019, 0.056, or 0.19 mg/ml of Metam Sodium in drinking water (0, 1.3, 3.9, or 12.0 mg/kg/day for males; 0, 2.3, 6.2, or 16.2 mg/kg/day for females) for 105 weeks. An additional 12 rats per sex per dose were designated for interim sacrifice at week 53.

A chronic carcinogenicity study in C57BL/10JfCD-1/Alpk mice received from the SPF Barriered Animal Breeding Unit of Zeneca Pharmaceuticals was conducted by Zeneca Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, United Kingdom, for the Metam Sodium Task Force, and dated April 20, 1994 (Report No. CTL/P/4095; Study No. PM0841; MRID No. 432335-01).

The study design allocated groups of 55 mice per sex to dose levels of 0, 0.019, 0.074, or 0.23 mg/ml of Metam Sodium in drinking water (0, 1.6, 6.5, or 27.7 mg/kg/day for males; 0, 2.3, 8.7, or 29.9 mg/kg/day for females) for 105 weeks.

Survival Analyses

The statistical evaluation of mortality indicated a significant decreasing trend with increasing doses of Metam Sodium in male rats. There were no significant incremental changes in mortality with increasing doses of Metam Sodium in female rats or male or female mice. See Tables 1 and 2 for rat mortality test results. See Tables 4 and 5 for mouse mortality test results.

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

Tumor Analyses

There were no statistically significant increasing trends in the tumor rates of male rats. However, there were significant differences in the pair-wise comparisons of the 1.3 and 3.9 mg/kg/day dose groups with the controls for hemangiosarcomas, with significance at $p < 0.05$ for the 1.3 mg/kg/day dose group and at $p < 0.01$ for the 3.9 mg/kg/day dose group.

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

Male mice had significant increasing trends, in addition to significant differences in the pair-wise comparisons of the 27.7 mg/kg/day dose group with the controls, for spleen and bone marrow (femur) angiosarcomas, angiosarcomas at all other sites, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined, all at $p < 0.01$. Male mice also had significant increasing trends in liver and subcutaneous tissue angiosarcomas at $p < 0.05$ and in bone marrow (spine) angiosarcomas at $p < 0.01$. There were significant differences in the pair-wise comparisons of the 1.6 and 27.7 mg/kg/day dose groups with the controls for liver angiosarcomas at $p < 0.05$ for the 1.6 mg/kg/day dose group and at $p < 0.01$ for the 27.7 mg/kg/day dose group.

Female mice had significant increasing trends in liver angiosarcomas, angiosarcomas at all sites combined, and angiomas and/or angiosarcomas combined, all at $p < 0.01$. Female mice also had a significant increasing trend, in addition to significant differences in the pair-wise comparisons of the 8.7 and 29.9 mg/kg/day dose groups with the controls, for spleen angiosarcomas, all at $p < 0.05$.

The statistical analyses of the male rats were based upon Peto's prevalence test since there was a statistically significant negative trend for mortality in male rats with increasing doses of Metam Sodium. The statistical analyses of the male and female mice 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, and Tables 6, 7, 8 and 9 for mouse tumor analysis results.

Table 1. Metam Sodium - Hsd/Ola: Wistar Tox Rat Study

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

	Weeks					
Dose (mg/kg/day)	1-26	27-52	53[i]	53-78	79-105[f]	Total
0	0/64	3/64	11/61	8/50	31/42	42/53 (79)*[n]
1.3	1/64	1/63	12/62	9/50	26/41	37/52 (71)
3.9	1/64	1/63	11/62	11/51	20/40	33/53 (62)
12.0	1/64	0/63	12/63	5/51	30/46	36/52 (69)*[n]

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

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

[n]Negative trend or negative change from control.

( )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. Metam Sodium - Hsd/Ola: Wistar Tox Rat Study

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

Dose (mg/kg/day)	Weeks 1-26	27-52	53[i]	53-78	79-105[f]	Total
0	1/64	1/63	10/62	7/52	19/45	28/54 (52)
2.3	0/64	4/64	11/60	8/49	16/41	28/53 (53)
6.2	0/64	2/64	12/62	6/50	21/44	29/52 (56)
16.2	1/64	2/63	12/61	4/49	16/45	23/52 (44)

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

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 105.

( )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. Metam Sodium - Hsd/Ola: Wistar Tox Rat Study

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

	Dose (mg/kg/day)			
	0	1.3	3.9	12.0
Hemangiomas	9[a]/50	3/50	4/51	8/51
(%)	(18)	(6)	(8)	(16)
p =	0.469[n]	0.950[n]	0.899[n]	0.688[n]
Hemangiosarcomas	0/47	3/49	8[b]/50	3/51
(%)	(0)	(6)	(16)	(6)
p =	0.414	0.017*	0.004**	0.073
Combined	9/50	6/50	11[c]/51	11/51
(%)	(18)	(12)	(22)	(22)
p =	0.375	0.713[n]	0.389	0.438

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

[a]First hemangioma observed at week 56, dose 0 mg/kg/day.

[b]First hemangiosarcoma observed at week 66, dose 3.9 mg/kg/day.

[c]One animal in the 3.9 mg/kg/day dose group had both a hemangioma and a hemangiosarcoma.

[n]Negative trend or negative change from control.

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. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

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

Dose (mg/kg/day)	Weeks 1-26	27-52	53-78	79-105[f]	Total
0	1/55	1/54	8/53	24/45	34/55 (62)
1.6	1/55	1/54	8/53	25/45	35/55 (64)
6.5	0/55	0/55	7/55	21/48	28/55 (51)
27.7	1/55	1/54	8/53	25/45	35/55 (64)

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

[f]Final sacrifice at week 105.

( )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. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

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

	Weeks				
Dose (mg/kg/day)	1-26	27-52	53-78	79-105[f]	Total
0	0/55	0/55	5/55	22/50	27/55 (49)
2.3	0/55	0/55	10/55	20/45	30/55 (55)
8.7	8/55	1/47	5/46	22/41	36/55 (65)
29.9	3/55	0/52	5/52	25/47	33/55 (60)

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

[f]Final sacrifice at week 105.

( )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. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study
Male Angiosarcoma Tumor Rates[+] and Exact
Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	1.6	6.5	27.7
Liver	1/52	8/52	5/55	10[a]/52
(%)	(2)	(15)	(9)	(19)
p =	0.023*	0.016*	0.116	0.004**
Spleen	6/53	3/53	10/55	21[b]/53
(%)	(11)	(6)	(18)	(40)
p =	0.000**	0.244[n]	0.233	0.001**
Bone Marrow	3/53	3/53	8[c]/55	15/53
(Femur) (%)	(6)	(6)	(15)	(28)
p =	0.000**	0.661	0.113	0.002**
Bone Marrow	2/53	0/53	0/55	7[d]/53
(Spine) (%)	(4)	(0)	(0)	(13)
p =	0.001**	0.248[n]	0.239[n]	0.080
Subcutaneous	1/53	1/53	2[e]/55	5/53
Tissue (%)	(2)	(2)	(4)	(9)
p =	0.020*	0.752	0.514	0.103
All Other Sites[#]	1/53	3/53	5[f]/55	9/53
(%)	(2)	(6)	(9)	(17)
p =	0.004**	0.309	0.112	0.008**
All Sites	7[g]/52	12[g]/52	12[g]/55	27[g]/52
Combined (%)	(13)	(23)	(22)	(52)
p =	0.000**	0.155	0.191	0.000**

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.
[n]Negative change from control.
[a]First liver angiosarcoma observed at week 68, dose 27.7 mg/kg/day.
[b]First spleen angiosarcoma observed at week 68, dose 27.7 mg/kg/day.
[c]First bone marrow (femur) angiosarcoma observed at week 69, dose 6.5 mg/kg/day.
[d]First bone marrow (spine) angiosarcoma observed at week 88, dose 27.7 mg/kg/day.
[e]First subcutaneous tissue angiosarcoma observed at week 71, dose 6.5 mg/kg/day.
[f]First angiosarcoma at any other site observed in the sternum at week 73, dose 6.5 mg/kg/day.
[g]Four, five, nine and eighteen animals in the 0, 1.6, 6.5, and 27.7

mg/kg/day dose groups, respectively, had angiosarcomas at multiple sites.

#Other sites include: abdominal cavity, aorta (adjacent tissue), bone (femur), heart, limb, lung, lymph node (mesenteric), mediastinum, mesentery, spinal cord, sternum, and thoracic cavity.

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. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

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

	Dose (mg/kg/day)			
	0	1.6	6.5	27.7
Angiomas[&]	2[a]/53	1/53	0/55	1/53
(%)	(4)	(2)	(0)	(2)
p =	0.378	0.500[n]	0.239[n]	0.500
Angiosarcomas[#]	7/52	12/52	12/55	27[b]/52
(%)	(13)	(23)	(22)	(52)
p =	0.000**	0.155	0.191	0.000**
Combined	8[c]/52	13/52	12/55	28/52
(%)	(15)	(25)	(22)	(54)
p =	0.000**	0.164	0.273	0.000**

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

[n]Negative change from control.

[a]First angioma observed at week 100, dose 0 mg/kg/day.
[b]First angiosarcoma observed at week 68, dose 27.7 mg/kg/day.
[c]One animal in the 0 mg/kg/day dose group had both an angioma and an angiosarcoma.

[&]Angioma sites include: aorta (adjacent tissue), lymph node (mesenteric), and subcutaneous tissue.

[#]Angiosarcoma sites include: abdominal cavity, aorta (adjacent tissue), bone (femur), bone marrow (femur), bone marrow (spine),

heart, limb, liver, lung, lymph node (mesenteric), mediastinum, mesentery, spinal cord, spleen, sternum, subcutaneous tissue, and thoracic cavity.

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 8. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

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

	Dose (mg/kg/day)			
	0	2.3	8.7	29.9
Liver	0/54	0/55	1/47	4[a]/52
(%)	(0)	(0)	(2)	(8)
p =	0.005**	1.000	0.465	0.055
Spleen	0/55	2/55	4[b]/47	5/52
(%)	(0)	(4)	(9)	(10)
p =	0.028*	0.248	0.042*	0.024*
All Other Sites[#]	4/55	2/55	6[c]/47	7/52
(%)	(7)	(4)	(13)	(13)
p =	0.070	0.339[n]	0.275	0.232
All Sites Combined	4/54	2[d]/55	6[e]/47	10[e]/52
(%)	(7)	(4)	(13)	(19)
p =	0.008**	0.331[n]	0.286	0.065

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 48.
[n]Negative change from control.

[a]First liver angiosarcoma observed at week 61, dose 29.9 mg/kg/day.
[b]First spleen angiosarcoma observed at week 48, dose 8.7 mg/kg/day.
[c]First angiosarcoma at any other site observed in the uterus at week 48, dose 8.7 mg/kg/day.
[d]Two animals in the 2.3 mg/kg/day dose group had angiosarcomas at multiple sites.
[e]Six animals in each of the 8.7 and 29.9 mg/kg/day dose groups had angiosarcomas at multiple sites.

#Other sites include: bone marrow (femur), bone marrow (spine), ear/Zymbal's gland, ileum, limb, mediastinum, ovary, salivary gland, spinal cord, sternum, subcutaneous tissue, and uterus.

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 9. Metam Sodium - C57BL/10JfCD-1/Alpk Mouse Study

Female Angioma and Angiosarcoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

	Dose (mg/kg/day)			
	0	2.3	8.7	29.9
Angiomas[&]	1/55	0/55	2[a]/47	2/52
(%)	(2)	(0)	(4)	(4)
p =	0.156	0.500	0.441	0.479
Angiosarcomas[#]	4/54	2/55	6[b]/47	10/52
(%)	(7)	(4)	(13)	(19)
p =	0.008**	0.331	0.286	0.065
Combined	5/54	2/55	8/47	11[c]/52
(%)	(9)	(4)	(17)	(21)
p =	0.009**	0.211[n]	0.194	0.075

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 48.

[n]Negative change from control.

[a]First angioma observed at week 87, dose 8.7 mg/kg/day.
[b]First angiosarcoma observed at week 48, dose 8.7 mg/kg/day.
[c]One animal in the 29.9 mg/kg/day dose group had both an angioma and an angiosarcoma.

[&]Angioma sites include: mammary gland, subcutaneous tissue, and uterus.

[#]Angiosarcoma sites include: bone marrow (femur), bone marrow (spine), ear/Zymbal's gland, ileum, limb, liver, mediastinum,

ovary, salivary gland, spinal cord, spleen, sternum, subcutaneous tissue, and uterus.

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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