

Reviewed by: Marcia van Gemert, Ph.D.
Head, Section III Tox. Branch (TS-769C)
Secondary reviewer: Theodore M. Farber, Ph.D.
Chief, Tox. Branch (TS-769C)

M. van Gemert 11.10.86
WJ Brock

DATA EVALUATION REPORT

STUDY TYPE: Chronic/Oncogenicity study in Rats TOX. CHEM. NO.: 573S
ACCESSION NUMBER: 263754, 263755 MRID NO.: ?
TEST MATERIAL: Harmony
SYNONYMS: INM-6316
STUDY NUMBER(S): 4980-001, #261-86
SPONSOR: Dupont de Nemours and Co.
TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine
TITLE OF REPORT: Long term feeding study in rats with INM-6316
AUTHOR(S): W.J. Brock, Ph.D.
REPORT ISSUED: June 26, 1986

CONCLUSIONS: There are several deficiencies in this study which will need to be corrected or explanations given.

1. Individual pathology sheets will need to be submitted.
2. An explanation will need to be given as to why several clinical chemistry parameters such as chloride, phosphorous, total bilirubin and creatinine phosphokinase were not investigated, especially when there were electrolyte effects.
3. An explanation will need to be given as to why ophthalmological examinations were not performed.
4. The clinical chemistry tables should be submitted in a clearer form.

There is a decrease in serum sodium levels at all dose levels tested with no no-effect level evident.
Classification: core-Supplementary

Special Review Criteria (40 CFR 154.7)

A. MATERIALS:

1. Test compound: INM-6316, Description not given,
 Batch # purity:
 INM-6316-20 95.6%
 INM-6316-25 98.0%
 INM 6316-25 98.2%

contaminants: list in CBI appendix

2. Test animals: Species: rat, Strain: Crl:CD@BR, Age: weanling,
 Weight: Males: 44-67 gms.
 Females: 27-58 gms.

Source: Charles River Breeding Laboratories, Kingston, N.Y.

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to the following test groups:

Test Group	Dose in diet (ppm)	Main Study 24 months		Interim Sac. 12 months	
		male	female	male	female
1 Cont.	0	62	62	10	10
2 Low (LDT)	25	62	62	10	10
3 Mid (MDT)	500	62	62	10	10
4 High (HDT)	2,500	62	62	10	10

2. Diet preparation

Diet was prepared weekly and stored at refrigerated temperature. Samples of treated food were analyzed for stability and concentration at day -1, 174, 245, 364, 525 553, 728.

Stability- samples included freshly prepared test diet, fresh diet stored for 24 hours and 10 days, and fresh diet stored refrigerated for 10 days.

Homogeneity- Samples were collected at three levels (bottom, middle and top) of mixing vessel for each dietary concentration.

Test diet preparation was changed to a corn oil suspension system on day 28, so an additional set of samples were collected on day 28.

Results -

After 28 days of diet mixing, it was clear that the compound was not being thoroughly mixed, since particles of compound could be seen throughout the diet. All subsequent diets were then prepared with corn oil.

2

Concentrations in various homogeneity samples were within 17% of nominally prepared concentrations. Also, there was little variability among the samples taken for stability within any particular dietary level. The stability data are on appended page 2, and show some variability in low dose diets stored at room temperature for 27 hours or 10 days. However, in spite of these variability changes, the main dietary concentrations were within 12% of the nominal concentration for each dose group.

3. Animals received food and water ad libitum.
4. Statistics - Statistical treatment of the data are presented on appended page 1.
5. Quality assurance statement was signed and numerous audit dates were documented.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected at least daily for signs of abnormal behavior, appearance, moribund or dead rats. At least once per week for the first 6 months and every other week thereafter until the end of the study each animal was handled and examined for changes in behavior and appearance.

Results:

1. Clinical observations: increased nasal discharge was noted in the mid and high dose males and all other signs were unremarkable. Data tables are appended.
2. Mortality: There was an increased mortality in the low dose females. However, this does not appear to be a treatment-related phenomenon. The data are appended in tabular form for reference.

2. Body weight

Animals were weighed weekly for 6 months, then once every other week until study termination.

Results:

There was a slight but significant decrease in high dose male body weights for the first 379 days on test (2-7% lower). They remained lower for the duration of the test (3.9%), although the effect was not statistically significant. Body weight gains for 0-182 days in the males were significantly lower ($p > 0.05$)

in the mid and high dose groups. However, for overall weight gain, 0-729 days, only the high dose group was marginally lower, without any statistical significance.

The mean body weights for females in the mid and high dose groups were slightly lower, with sporadically significant decreases in some weeks. However, there were no significant decreases in body weight gain at any of the time periods measured. Data from the study text are appended.

3. Food consumption and food efficiency

Consumption was determined weekly, and mean daily diet consumption was calculated. Efficiency and compound intake were calculated from the consumption and body weight gain data.

Results:

1. Food consumption: No treatment-related effects were seen in food consumption.
2. There was a decrease in food efficiency in the mid and high dose males, in the time period 0-182 days, corresponding to the decreased body weight gains seen in these animals. The results, however, were not statistically significant. The data are appended for reference.

4. Ophthalmological examinations

Examinations were not performed on any animals.

5. Blood was collected before treatment and at 3,6,9,12,18,21 and 24 months for hematology and clinical analysis from 10 animals/group. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB conc.(MCHC)
	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*	X	Reticulocyte count
	Blood Clotting Measurements	X	Bone Marrow smears were prepared
	(Thromboplastin time)		but not evaluated
	(Prothrombin time)		
	(Clotting time)		

* Required for subchronic and chronic studies

Results: Comments are contained in the results section for clinical chemistry.

4

b. Clinical Chemistry

<p><u>X</u></p> <p>Electrolytes:</p> <p>X Calcium*</p> <p> Chloride*</p> <p> Magnesium</p> <p> Phosphorous*</p> <p>X Potassium*</p> <p>X Sodium*</p> <p>Enzymes</p> <p>X Alkaline phosphatase</p> <p> Cholinesterase#</p> <p> Creatinine phosphokinase**</p> <p> Lactic acid dehydrogenase</p> <p>X Serum alanine aminotransferase (also SGPT)*</p> <p>X Serum aspartate aminotransferase (also SGOT)*</p> <p> gamma glutamyl transferase</p> <p> glutamate dehydrogenase</p>	<p><u>X</u></p> <p>Other:</p> <p>X Albumin*</p> <p>X Blood creatinine*</p> <p>X Blood urea nitrogen*</p> <p>X Cholesterol*</p> <p> Globulins</p> <p>X Glucose*</p> <p> Total Bilirubin*</p> <p>X Total Serum Protein*</p> <p> Triglycerides</p> <p> Serum protein electrophoresis</p>
---	---

- * Required for subchronic and chronic studies
- # Should be required for OP
- ° Not required for subchronic studies

The summary tables and statistical summary tables of all the clinical chemistry and hematological parameters were very confusing follow. It is not clear from the statistical summary tables (tables I and II) which parameters are statistically significant and what the p values are. Some parameters show groups with arrows and (+) and some are missing the (+). This is not clearly defined in the table legend. This table will need to be clarified. Preferably, tables I and II could be combined with tables 3,4,5 and 6.

From the summary tables it appears that there are decreased sodium levels in the high dose males at 9, 12, 18 and 24 months. In the mid-dose males sodium levels were decreased at 9, 18 and 24 months and the low dose at 24 months.

In the females, sodium is decreased in the high dose at 9, 12, 18, 21 and 24 months, the mid-dose at 9, 12 and 18 months, and the low dose at 12 months.

Hematocrit also appears decreased in the high dose females at 9 and 24 months.

It appears that there may be no no-effect level for decreased serum sodium. (see statistical summary table submitted by Dupont on the appended page) Better tables would clarify this situation. It isn't clear why all the recommended clinical chemistry parameters were not investigated, such as chloride, phosphorous, creatinine phosphokinase, and total bilirubin. These have been recommended in the guidelines as clinical chemistry parameters to be investigated. It is especially unusual since there were some electrolyte changes, eg. sodium levels, at all doses tested.

6. Urinalysis

Urine was collected from fasted animals at 3,6,9,12,18, 21 and 24 months from 10 animals/group in 24 hour samples in metabolism cages. The CHECKED (X) parameters were examined.

<table border="0"> <tr><td>X</td><td> </td><td></td></tr> <tr><td>X</td><td> </td><td>Appearance*</td></tr> <tr><td>X</td><td> </td><td>Volume*</td></tr> <tr><td></td><td> </td><td>Specific gravity*</td></tr> <tr><td>X</td><td> </td><td>pH</td></tr> <tr><td>X</td><td> </td><td>Sediment (microscopic)*</td></tr> <tr><td>X</td><td> </td><td>Protein*</td></tr> <tr><td>X</td><td> </td><td>Osmolality</td></tr> </table>	X			X		Appearance*	X		Volume*			Specific gravity*	X		pH	X		Sediment (microscopic)*	X		Protein*	X		Osmolality	<table border="0"> <tr><td>X</td><td> </td><td>Glucose*</td></tr> <tr><td>X</td><td> </td><td>Ketones*</td></tr> <tr><td>X</td><td> </td><td>Bilirubin*</td></tr> <tr><td>X</td><td> </td><td>Blood*</td></tr> <tr><td></td><td> </td><td>Nitrate</td></tr> <tr><td>X</td><td> </td><td>Urobilinogen</td></tr> </table>	X		Glucose*	X		Ketones*	X		Bilirubin*	X		Blood*			Nitrate	X		Urobilinogen
X																																											
X		Appearance*																																									
X		Volume*																																									
		Specific gravity*																																									
X		pH																																									
X		Sediment (microscopic)*																																									
X		Protein*																																									
X		Osmolality																																									
X		Glucose*																																									
X		Ketones*																																									
X		Bilirubin*																																									
X		Blood*																																									
		Nitrate																																									
X		Urobilinogen																																									

- * Required for chronic studies
- ° Not required for subchronic studies

Urinalysis tables are in the same shape as those for clinical chemistry and hematology. It doesn't appear, however, that there were any compound-related effects of note.

7. Sacrifice and Pathology -

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

<table border="0"> <tr><td>X</td><td> </td><td>Digestive system</td></tr> <tr><td>X</td><td> </td><td>Tongue</td></tr> <tr><td>X</td><td> </td><td>.Salivary glands*</td></tr> <tr><td>X</td><td> </td><td>.Esophagus*</td></tr> <tr><td>X</td><td> </td><td>.Stomach*</td></tr> <tr><td>X</td><td> </td><td>.Duodenum*</td></tr> <tr><td>X</td><td> </td><td>.Jejunum*</td></tr> <tr><td>X</td><td> </td><td>.Ileum*</td></tr> <tr><td>X</td><td> </td><td>.Cecum*</td></tr> <tr><td>X</td><td> </td><td>.Colon*</td></tr> <tr><td>X</td><td> </td><td>.Rectum*</td></tr> <tr><td>XX</td><td> </td><td>.Liver*†</td></tr> <tr><td></td><td> </td><td>Gall bladder**</td></tr> <tr><td>X</td><td> </td><td>.Pancreas*</td></tr> <tr><td></td><td> </td><td>Respiratory</td></tr> <tr><td>X</td><td> </td><td>.Trachea*</td></tr> <tr><td>X</td><td> </td><td>.Lung*</td></tr> <tr><td></td><td> </td><td>Nose°</td></tr> </table>	X		Digestive system	X		Tongue	X		.Salivary glands*	X		.Esophagus*	X		.Stomach*	X		.Duodenum*	X		.Jejunum*	X		.Ileum*	X		.Cecum*	X		.Colon*	X		.Rectum*	XX		.Liver*†			Gall bladder**	X		.Pancreas*			Respiratory	X		.Trachea*	X		.Lung*			Nose°	<table border="0"> <tr><td>X</td><td> </td><td>Cardiovasc./Hemat.</td></tr> <tr><td>X</td><td> </td><td>.Aorta*</td></tr> <tr><td>XX</td><td> </td><td>.Heart*</td></tr> <tr><td>X</td><td> </td><td>.Bone marrow*</td></tr> <tr><td>X</td><td> </td><td>.Lymph nodes*</td></tr> <tr><td>XX</td><td> </td><td>.Spleen*</td></tr> <tr><td>X</td><td> </td><td>.Thymus*</td></tr> <tr><td></td><td> </td><td>Urogenital</td></tr> <tr><td>XX</td><td> </td><td>.Kidneys*†</td></tr> <tr><td>X</td><td> </td><td>.Urinary bladder*</td></tr> <tr><td>XX</td><td> </td><td>.Testes*†</td></tr> <tr><td>X</td><td> </td><td>Epididymides</td></tr> <tr><td>X</td><td> </td><td>Prostate</td></tr> <tr><td>X</td><td> </td><td>Seminal vesicle</td></tr> <tr><td>X</td><td> </td><td>Ovaries*†</td></tr> <tr><td>X</td><td> </td><td>.Uterus*</td></tr> <tr><td>X</td><td> </td><td>Cervix</td></tr> <tr><td>X</td><td> </td><td>Vagina</td></tr> </table>	X		Cardiovasc./Hemat.	X		.Aorta*	XX		.Heart*	X		.Bone marrow*	X		.Lymph nodes*	XX		.Spleen*	X		.Thymus*			Urogenital	XX		.Kidneys*†	X		.Urinary bladder*	XX		.Testes*†	X		Epididymides	X		Prostate	X		Seminal vesicle	X		Ovaries*†	X		.Uterus*	X		Cervix	X		Vagina	<table border="0"> <tr><td>X</td><td> </td><td>Neurologic</td></tr> <tr><td>XX</td><td> </td><td>.Brain*†</td></tr> <tr><td>X</td><td> </td><td>Periph. nerve**</td></tr> <tr><td>X</td><td> </td><td>Spinal cord (3 levels)**</td></tr> <tr><td>X</td><td> </td><td>.Pituitary*</td></tr> <tr><td>X</td><td> </td><td>Eyes (optic n.)*#</td></tr> <tr><td></td><td> </td><td>Glandular</td></tr> <tr><td>X</td><td> </td><td>.Adrenals*</td></tr> <tr><td></td><td> </td><td>Lacrimal gland#</td></tr> <tr><td>X</td><td> </td><td>Mammary gland**</td></tr> <tr><td>X</td><td> </td><td>.Parathyroids*††</td></tr> <tr><td>X</td><td> </td><td>.Thyroids*††</td></tr> <tr><td></td><td> </td><td>Other</td></tr> <tr><td>X</td><td> </td><td>Bone**</td></tr> <tr><td>X</td><td> </td><td>Skeletal muscle**</td></tr> <tr><td>X</td><td> </td><td>Skin**</td></tr> <tr><td>X</td><td> </td><td>All gross lesions</td></tr> <tr><td></td><td> </td><td>and masses*</td></tr> <tr><td>X</td><td> </td><td>Hardarian gland</td></tr> </table>	X		Neurologic	XX		.Brain*†	X		Periph. nerve**	X		Spinal cord (3 levels)**	X		.Pituitary*	X		Eyes (optic n.)*#			Glandular	X		.Adrenals*			Lacrimal gland#	X		Mammary gland**	X		.Parathyroids*††	X		.Thyroids*††			Other	X		Bone**	X		Skeletal muscle**	X		Skin**	X		All gross lesions			and masses*	X		Hardarian gland
X		Digestive system																																																																																																																																																																					
X		Tongue																																																																																																																																																																					
X		.Salivary glands*																																																																																																																																																																					
X		.Esophagus*																																																																																																																																																																					
X		.Stomach*																																																																																																																																																																					
X		.Duodenum*																																																																																																																																																																					
X		.Jejunum*																																																																																																																																																																					
X		.Ileum*																																																																																																																																																																					
X		.Cecum*																																																																																																																																																																					
X		.Colon*																																																																																																																																																																					
X		.Rectum*																																																																																																																																																																					
XX		.Liver*†																																																																																																																																																																					
		Gall bladder**																																																																																																																																																																					
X		.Pancreas*																																																																																																																																																																					
		Respiratory																																																																																																																																																																					
X		.Trachea*																																																																																																																																																																					
X		.Lung*																																																																																																																																																																					
		Nose°																																																																																																																																																																					
X		Cardiovasc./Hemat.																																																																																																																																																																					
X		.Aorta*																																																																																																																																																																					
XX		.Heart*																																																																																																																																																																					
X		.Bone marrow*																																																																																																																																																																					
X		.Lymph nodes*																																																																																																																																																																					
XX		.Spleen*																																																																																																																																																																					
X		.Thymus*																																																																																																																																																																					
		Urogenital																																																																																																																																																																					
XX		.Kidneys*†																																																																																																																																																																					
X		.Urinary bladder*																																																																																																																																																																					
XX		.Testes*†																																																																																																																																																																					
X		Epididymides																																																																																																																																																																					
X		Prostate																																																																																																																																																																					
X		Seminal vesicle																																																																																																																																																																					
X		Ovaries*†																																																																																																																																																																					
X		.Uterus*																																																																																																																																																																					
X		Cervix																																																																																																																																																																					
X		Vagina																																																																																																																																																																					
X		Neurologic																																																																																																																																																																					
XX		.Brain*†																																																																																																																																																																					
X		Periph. nerve**																																																																																																																																																																					
X		Spinal cord (3 levels)**																																																																																																																																																																					
X		.Pituitary*																																																																																																																																																																					
X		Eyes (optic n.)*#																																																																																																																																																																					
		Glandular																																																																																																																																																																					
X		.Adrenals*																																																																																																																																																																					
		Lacrimal gland#																																																																																																																																																																					
X		Mammary gland**																																																																																																																																																																					
X		.Parathyroids*††																																																																																																																																																																					
X		.Thyroids*††																																																																																																																																																																					
		Other																																																																																																																																																																					
X		Bone**																																																																																																																																																																					
X		Skeletal muscle**																																																																																																																																																																					
X		Skin**																																																																																																																																																																					
X		All gross lesions																																																																																																																																																																					
		and masses*																																																																																																																																																																					
X		Hardarian gland																																																																																																																																																																					

- * Required for subchronic and chronic studies
- ° Required for chronic inhalation
- # In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
- † Organ weights required in subchronic and chronic studies
- †† Organ weight required for non-rodent studies

6

Animals that were sacrificed were anaesthetized with chloroform and sacrificed by exanguination. All tissues listed above were examined in the control and high dose groups and in all rats sacrificed in extremis or found dead. Lungs, liver and kidneys and all gross lesions from rats in the low and intermediate groups were examined microscopically.

Results:

a. Organ weight

There was a statistically significant increase in relative heart weight in the high dose and an increase in relative kidney weights in the mid and high dose males at the one year sacrifice. (see appended pages) Other organ weights in both males and females at one year were not significantly different from controls.

There were no statistically significant changes in either absolute or relative organ weights in the males or females at the 2-year scheduled termination of the study.

b. Gross pathology

There did not appear to be any gross changes in pathology, although the individual animal pathology sheets were not submitted with the study. Therefore, a final decision concerning gross pathology will not be rendered until the individual pathology sheets are submitted.

c. Microscopic pathology

1) Non-neoplastic - The summary tables and text report that there were no treatment-related effects of the compound.

2) Neoplastic- There was a significant increase reported in the study text in the mid and high dose females of "total tumors". However, this is not a valid carcinogenic end point and will not be considered further. Before any definitive judgment can be made concerning the carcinogenic potential of this compound, individual pathology sheets will have to be submitted.

D. DISCUSSION:

There are several major deficiencies in this study, and these will need to be corrected.

1. Individual pathology sheets on each animal will need to be submitted to verify the pathology summary tables.
2. An explanation will need to be given as to why several clinical chemistry parameters such as chloride, phosphorous, total bilirubin and creatinine phosphokinase were not investigated, especially when there were effects on electrolytes.
3. An explanation should be given as to why no ophthalmological exams were performed.
4. The clinical chemistry tables should be submitted in a clearer form.

There is a decrease in serum sodium levels at all dose levels with no no-effect level evident. NOEL = less than 25 ppm.

7

H. Residue Analyses

Tissue samples (brain, liver, kidney, spleen, muscle, testis, and fat) and blood were collected from ten rats per group sacrificed at one and two years. Urine and feces samples were also collected from ten rats per group at one and two years. Urine collected for residue analyses at the 24-month clinical evaluation was inadvertently discarded. All samples were pooled by test group, frozen, and sent to the Agricultural Products Department for residue analyses. The results of any residue analyses will be reported by the Agricultural Products Department.

I. Statistical Analyses

Body weights, body weight gains, absolute and relative organ weights, and clinical laboratory measurements were analyzed by a one-way analysis of variance. When the test for differences among group means (F-test) was significant, pairwise comparisons were made between control and test groups. For body weights and weight gains, these comparisons were made with the least significant difference (LSD) test. The clinical laboratory measurements were compared by Kruskal-Wallis, Mann-Whitney U, and Dunnett's tests. The Bartlett's test for homogeneity of variances was performed on organ weights and clinical laboratory measurements. Organ weights were examined for pairwise comparisons by LSD and Dunnett's tests and by a test for linear trend. Tumor incidence and clinical observations were analyzed by Fisher's Exact test with a Bonferroni correction. Tests for the comparison of means were considered significant at the $p < 0.05$ probability level.

H# 15,172
 MR 4980
 HC 34

TABLE 12

SUMMARY OF CLINICAL OBSERVATIONS IN MALE RATS FED FOR TWO YEARS
 WITH DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

GROUP: CONCENTRATION (ppm):	I 0	III 25	V 500	VII 2,500
<hr/>				
<u>OBSERVATION^a</u>				
ABNORMAL GAIT	0	1 (728)	1 (659)	0
ALOPECIA	32 (477)	43 (477)	38 (505)	42 (554)
BENT TAIL	0	0	1 (267)	0
BLOATED	14 (547)	17 (365)	18 (407)	11 (379)
COLORLED DISCHARGE EYE(S) ^b	24 (498)	19 (500)	30 (540)	28 (533)
COLORLED DISCHARGE MOUTH	2 (508)	1 (154)	1 (119)	1 (119)
COLORLED DISCHARGE NOSE ^c	27 (175)	36 (144)	43 (133)*	38 (147)*
COLORLED DISCHARGE PENIS	0	1 (126)	0	0
CORNEAL OPACITY ^d	2 (501)	7 (610)	3 (547)	3 (500)
CUT TOE(S)	1 (589)	0	2 (715)	0
CYANOTIC	0	0	0	0
DIARRHEA	36 (428)	32 (519)	26 (484)	18 (533)
END OF TAIL MISSING ^e	2 (277)	1 (175)	3 (421)	0
ENOPHTHALMUS	0	0	0	0
EXOPHTHALMUS	1 (407)	1 (701)	2 (638)	1 (729)
HUNCHED OVER	3 (469)	5 (500)	1 (407)	5 (589)
HYPERACTIVE	1 (281)	0	1 (281)	0
HYPERREACTIVE	16 (337)	7 (154)	12 (371)	15 (196)
IMMOBILE LEG(S) ^f	0	4 (685)	1 (724)	2 (465)
IRREGULAR RESPIRATION ^g	4 (449)	2 (239)	2 (514)	2 (510)
LEANS TO SIDE ^h	0	0	1 (637)	0
MISSHAPEN EAR(S) ⁱ	2 (554)	0	0	0
MISSHAPEN SNOUT	0	0	0	0
PALLOR	3 (561)	7 (687)	0	5 (589)
RUFFLED FUR	5 (323)	21 (267)	9 (267)	6 (260)
SKIN SORE(S)	45 (449)	41 (295)	53 (323)	47 (463)
STAINED AND/OR WET FUR ^j	43 (365)	49 (267)	50 (386)	39 (379)
STAINED AND/OR WET UNDER BODY ^k	35 (617)	27 (505)	28 (624)	24 (631)

9

H# 15,172
MR 4980
HC 34

TABLE 14

INCIDENCE OF MORTALITY AMONG MALE AND FEMALE RATS FED FOR TWO YEARS
WITH DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316^a

<u>DIETARY CONCENTRATION (ppm)</u>	<u>NUMBER OF DEATHS (% MORTALITY)^b</u>	
	<u>MALES</u>	<u>FEMALES</u>
0	44 (71%) ^c	35 (56%) ^d
25	39 (63%) ^e	47 (76%) ^{f*}
500	39 (63%) ^g	30 (48%) ^h
2,500	32 (52%) ⁱ	40 (65%) ^j

- ^a This table does not include any scheduled deaths. All rats were found dead except where noted.
- ^b % Mortality = (number of deaths per group/62 rats per group X 100).
- ^c Includes 16 rats sacrificed in extremis.
- ^d Includes 14 rats sacrificed in extremis.
- ^e Includes 11 rats sacrificed in extremis.
- ^f Includes 24 rats sacrificed in extremis.
- ^g Includes 15 rats sacrificed in extremis.
- ^h Includes 13 rats sacrificed in extremis.
- ⁱ Includes 9 rats sacrificed in extremis.
- ^j Includes 15 rats sacrificed in extremis.
- * Significantly different ($p \leq 0.05$) from the control group by Fisher's Exact test.

H# 15,172
MR 4980
HC 34

TABLE 1
SUMMARY OF DIETARY ANALYSES FOR INM-6316 DURING
THE TWO-YEAR FEEDING STUDY IN RATS

<u>Storage Condition</u>	<u>Nominal Dietary Concentration (ppm)^a</u>		
	<u>25</u>	<u>500</u>	<u>2,500</u>
Fresh Frozen	25 ₊₁ ^b (100%) ^c	520 ₊₃₆ (104%)	2637 ₊₁₈₆ (105%)
24-Hour Room Temperature	23 ₊₃ (92%)	515 ₊₂₁ (103%)	2600 ₊₂₂₀ (104%)
10-Day Room Temperature	22 ₊₃ (88%)	463 ₊₃₀ (93%)	2450 ₊₂₄₁ (98%)
10-Day Refrigerated	25 ₊₁ (100%)	520 ₊₄₇ (104%)	2605 ₊₂₂₇ (104%)

^a The results of diet analyses collected at the initiation of this study (day -1) are not included in this table since the method of diet preparation was changed to include corn oil. The data presented in this table represent those diets prepared with corn oil. Each value is the mean (+S.D.), and the results were not corrected for recovery which ranged from 90-120%.

^b The results of analyses of diet samples collected on day 525 are not included in this value since INM-6316 was not detected.

^c The number in parentheses represents the percent of nominal INM-6316 dietary concentration prepared.

H# 15,172
 MR 4980
 HC 34

TABLE 2

MEAN BODY WEIGHTS OF MALE RATS FED FOR TWO YEARS WITH
 DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

MEAN BODY WEIGHTS (g)				
GROUP: CONCENTRATION (ppm):	I 0	III 25	V 500	VII 2,500
DAYS ON TEST				
0	194.5	193.7	192.8	191.6
7	249.5	248.4	245.5	243.4*
14	299.1	297.8	294.4	289.4*
21	337.5	336.7	332.6	325.7*
28	372.6	372.1	366.1	356.6*
35	400.1	400.7	392.3	380.7*
42	422.6	420.8	412.9	396.5*
49	444.7	440.9	433.5	418.3*
56	464.0	459.2	449.8*	435.8*
63	482.2	479.9	467.5*	452.5*
70	492.6	491.2	480.7	464.7*
77	505.6	503.3	492.7	477.1*
84	516.6	512.6	501.1	484.2*
91	525.8	521.0	506.7*	491.7*
98	534.3	531.7	518.8	503.6*
105	544.7	539.2	527.5*	509.7*
112	552.8	549.2	534.6*	519.7*
119	562.1	557.0	538.3*	525.3*
126	568.1	564.5	543.7*	532.7*
133	579.6	573.2	554.2*	541.0*
140	583.5	578.0	559.0*	543.1*
147	589.6	584.0	565.4*	548.3*
154	598.4	592.3	571.7*	559.5*
161	602.2	597.1	578.0*	564.2*
168	605.5	602.4	585.8	569.5*
175	611.1	608.2	587.1*	569.5*
182	620.2	617.3	592.5*	578.7*
196	631.3	627.4	605.7*	591.8*
210	643.8	644.1	620.7*	604.7*
224	654.9	653.9	629.0*	610.4*
239	671.2	665.2	641.5*	622.7*
253	678.7	671.5	648.9*	629.9*
267	685.8	680.4	657.4*	638.0*
281	691.1	685.1	664.9	649.9*

12

H# 15,172
 MR 4980
 HC 34

TABLE 2 (Continued)

MEAN BODY WEIGHTS OF MALE RATS FED FOR TWO YEARS WITH
 DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHTS (g)			
	<u>I</u> 0	<u>III</u> 25	<u>V</u> 500	<u>VII</u> 2,500
DAYS ON TEST				
295	701.1	699.8	677.3	656.6*
309	711.9	709.0	686.2	665.1*
323	716.8	715.8	693.1	671.2*
337	725.0	721.5	702.4	681.1*
351	723.5	722.6	703.5	681.7*
365	740.8	732.1	717.1	695.4*
379	740.4	750.6	730.7	704.2*
393	746.8	757.4	739.8	711.6
407	749.7	760.0	746.1	719.2
421	754.6	767.7	754.5	725.5
435	765.6	771.9	764.2	731.1
449	769.2	768.6	764.8	735.4
463	765.5	761.6	767.9	736.9
477	775.2	760.7	778.7	748.0
491	774.0	762.1	780.2	750.6
505	774.4	771.6	785.1	752.3
519	781.0	779.9	788.5	760.3
533	787.5	778.4	790.3	752.7
547	779.1	775.8	784.7	755.9
561	771.3	794.2	773.0	759.0
575	770.8	788.1	798.5	748.5
589	751.1	804.7	794.1	735.1
603	754.4	798.5	795.8	726.0
617	764.2	792.0	775.3	734.7
631	761.8	797.3	781.1	740.5
645	751.2	799.3	779.6	726.5
659	731.0	790.5	773.7	709.8
673	746.6	777.6	766.7	717.8
687	733.8	756.9	766.1	697.1
701	713.6	748.3	746.0	676.8
715	728.9	718.8	723.6	666.8
729	706.1	687.7	727.1	671.3

*Different from control at $p < 0.05$ level of significance.

13

H# 15,172
 MR 4980
 HC 34

TABLE 3

MEAN BODY WEIGHTS OF FEMALE RATS FED FOR TWO YEARS WITH
 DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

DAYS ON TEST	CONCENTRATION	GROUP: (ppm):	MEAN BODY WEIGHTS (g)			
			II 0	IV 25	VI 500	VIII 2,500
0			138.8	138.9	138.3	137.4
7			159.1	159.3	157.7	156.2
14			176.9	176.0	176.3	175.0
21			191.4	190.8	191.1	188.5
28			204.7	206.6	204.9	202.7
35			216.0	216.8	215.6	212.6
42			224.5	224.9	224.2	220.7
49			232.0	231.0	232.0	225.0
56			234.6	235.7	236.8	233.0
63			245.2	245.2	243.5	237.6
70			251.2	252.0	250.6	241.4*
77			255.5	257.8	256.6	248.3
84			256.4	260.6	258.9	249.6
91			259.8	264.5	262.1	251.9
98			267.1	271.8	269.1	257.6*
105			271.0	274.6	272.0	262.8
112			274.3	279.4	275.6	265.6
119			278.9	284.5	278.6	266.8*
126			285.2	289.1	283.4	271.8*
133			287.6	291.5	286.6	275.1*
140			288.3	294.8	289.2	277.5*
147			289.5	297.2	291.8	280.2
154			296.4	302.7	297.1	285.5
161			297.3	301.6	298.1	288.5
168			304.4	309.6	302.9	293.8
175			305.3	309.3	305.7	295.5
182			311.0	313.9	311.9	299.5
196			320.2	328.2	320.8	308.5
210			328.2	333.6	327.9	315.1
224			332.6	343.4	335.4	320.9
239			343.1	354.5	342.9	331.0
253			345.5	360.9	347.9	336.2
267			353.7	369.7	356.1	345.0
281			361.0	375.4	356.5	348.0

14

H# 15,172
MR 4980
HC 34

TABLE 3 (Continued)

MEAN BODY WEIGHTS OF FEMALE RATS FED FOR TWO YEARS WITH
DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

DAYS ON TEST	GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHTS (g)			
		II 0	IV 25	VI 500	VIII 2,500
295		369.5	384.5	367.8	360.1
309		377.5	399.8*	377.5	368.9
323		386.4	411.9*	387.8	377.3
337		393.0	417.6*	395.2	382.8
351		406.1	431.9*	407.4	392.7
365		409.0	436.6*	411.0	398.3
379		419.3	457.2*	425.2	405.1
393		431.4	468.1*	434.9	410.3
407		438.0	474.8*	442.4	421.9
421		444.4	480.4*	446.3	426.0
435		450.3	491.8*	448.7	433.0
449		454.6	492.7*	452.9	435.1
463		460.5	497.2*	454.7	439.1
477		464.6	503.1*	463.1	442.3
491		465.5	502.9	464.6	443.2
505		476.6	516.2*	470.5	453.8
519		484.6	517.0	474.1	459.7
533		483.0	515.5	473.2	453.8
547		480.6	513.4	472.5	455.7
561		478.3	502.7	470.7	463.0
575		487.6	510.6	460.7	457.2
589		489.2	510.2	458.6	452.4
603		496.0	504.8	458.6	457.3
617		500.8	505.3	463.4	472.2
631		506.2	501.3	478.0	473.5
645		492.5	492.4	476.4	474.1
659		489.2	494.4	477.4	487.5
673		486.3	511.3	470.9	479.1
687		489.6	507.1	461.3	461.7
701		493.0	525.0	459.5	451.0
715		490.5	510.3	457.2	460.1
729		478.8	495.4	449.8	468.2

*Different from control at $p < 0.05$ level of significance.

15

H# 15,172
 MR 4980
 HC 34

TABLE 4

MEAN BODY WEIGHT GAINS OF MALE RATS FED FOR TWO YEARS WITH
 DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

		MEAN BODY WEIGHT GAINS (g)			
CONCENTRATION	GROUP: (ppm):	I 0	III 25	V 500	VII 2,500
DAYS ON TEST					
0- 7		55.0	54.6	52.7*	51.8*
7- 14		49.6	49.4	48.9	46.0*
14- 21		38.4	38.9	38.2	36.4
21- 28		35.1	35.4	33.5	30.9*
28- 35		27.5	28.6	26.2	24.1*
35- 42		22.5	20.1	20.6	15.8*
42- 49		22.2	20.2	20.7	21.8
49- 56		19.3	18.3	16.2	17.5
56- 63		18.2	20.7	17.7	16.7
63- 70		10.3	11.3	13.3	12.3
70- 77		13.1	12.1	12.3	12.4
77- 84		11.0	9.3	8.4	7.0
84- 91		9.1	8.3	5.6	7.5
91- 98		8.5	10.8*	12.1*	11.9*
98-105		10.4	7.5*	8.7	6.2*
105-112		8.1	10.0	7.1	10.0
112-119		9.4	7.8	3.7*	5.6*
119-126		6.0	7.5	5.4	6.7
126-133		11.4	8.7	10.4	8.3
133-140		3.9	4.8	4.8	2.2
140-147		6.2	6.0	6.4	5.2
147-154		8.8	8.3	6.2	11.2
154-161		3.7	4.8	6.4	4.7
161-168		3.3	5.3	7.7	5.4
168-175		5.6	5.8	1.3	0.0*
175-182		9.2	9.1	5.4	9.2
182-196		11.1	10.1	13.2	13.1
196-210		12.5	16.7*	15.0	12.9
210-224		11.0	9.8	8.5	5.7*
224-239		16.4	11.3	12.4	12.6
239-253		7.5	6.3	7.4	7.2
253-267		7.1	9.0	8.5	8.0
267-281		5.3	4.7	7.5	11.9*

16

H# 15,172
MR 4980
HC. 34

TABLE 4 (Continued)

MEAN BODY WEIGHT GAINS OF MALE RATS FED FOR TWO YEARS WITH
DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

DAYS ON TEST	GROUP: CONCENTRATION (ppm):	MEAN BODY WEIGHT GAINS (g)			
		I 0	III 25	V 500	VII 2,500
281-295		12.6	14.6	12.4	6.7*
295-309		10.8	9.2	8.9	8.5
309-323		4.9	6.8	5.9	6.1
323-337		8.2	5.7	9.3	9.9
337-351		-1.4	1.1	1.2	0.6
351-365		17.2	9.5	13.6	13.7
365-379		8.0	9.9	14.0*	11.3
379-393		6.4	6.9	9.1	7.4
393-407		2.9	4.7	6.3	7.6
407-421		4.9	7.7	7.4	6.0
421-435		2.8	5.2	9.7*	5.6
435-449		3.6	-3.3	0.6	4.3
449-463		-3.7	-8.5	3.1	1.5
463-477		0.7	-0.9	5.0	4.4
477-491		-1.2	-3.2	0.1	2.6
491-505		-1.7	-4.3	5.0	0.9
505-519		-5.2	-0.1	2.4	5.1
519-533		-8.4	-3.9	-4.0	-7.6
533-547		-3.8	-2.6	-5.6	-0.5
547-561		-7.8	-2.2	-8.7	-4.1
561-575		-6.1	-6.1	-6.0	-10.5
575-589		-17.2	-2.8	-4.4	-13.4
589-603		-10.8	-5.4	-8.4	-15.4
603-617		-4.2	-11.6	-14.7	-14.8
617-631		-2.4	-6.9	-8.9	-3.7
631-645		-15.9	-13.1	-15.5	-17.1
645-659		-21.7	-10.9	-9.4	-15.5
659-673		-18.7	-12.9	-12.8	-14.2
673-687		-24.0	-25.5	-14.5	-21.9
687-701		-24.7	-17.1	-20.1	-26.0
701-715		-18.5	-21.8	-22.3	-27.7
715-729		-22.8	-34.5	-28.9	-19.6
0-182		425.7	423.6	399.6*	386.7*
182-365		122.6	114.8	125.6	117.2
365-729		-3.3	-26.1	48.8	-16.6
0-729		510.5	493.7	534.3	478.0

*Different from control at $p < 0.05$ level of significance.

H# 15,172
MR 4980
HC 34

TABLE 5

MEAN BODY WEIGHT GAINS OF FEMALE RATS FED FOR TWO YEARS WITH
DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

		MEAN BODY WEIGHT GAINS (g)			
GROUP:		II	IV	VI	VIII
CONCENTRATION (ppm):		0	25	500	2,500
DAYS ON TEST					
0- 7		20.3	20.4	19.4	18.8
7- 14		17.8	16.7	18.6	18.8
14- 21		14.5	14.8	14.8	13.5
21- 28		13.3	15.8*	13.8	14.3
28- 35		11.3	10.1	10.7	9.9
35- 42		8.5	8.1	8.6	8.1
42- 49		7.4	6.2	7.8	4.3*
49- 56		2.6	4.7	4.8	8.0*
56- 63		10.6	9.5	6.7*	4.5*
63- 70		5.9	6.8	7.1	3.9*
70- 77		4.3	5.8	6.0	6.9
77- 84		0.9	2.8	2.3	1.3
84- 91		3.4	3.9	3.2	2.2
91- 98		7.3	7.3	7.1	5.7
98-105		3.9	2.8	2.8	5.2
105-112		3.4	4.8	3.7	2.8
112-119		4.5	5.1	3.0	1.3*
119-126		6.3	4.6	4.8	5.0
126-133		2.4	2.4	3.2	3.3
133-140		0.7	3.3	2.6	2.5
140-147		1.3	2.4	2.6	2.6
147-154		6.9	5.5	5.3	5.4
154-161		1.0	-1.1	0.9	3.0
161-168		4.6	8.0	4.9	5.3
168-175		0.9	-0.3	1.2	1.7
175-182		5.1	4.6	6.1	4.0
182-196		9.2	14.3*	8.9	9.0
196-210		8.0	5.4	7.2	6.6
210-224		4.4	9.8*	7.5*	5.9
224-239		10.5	11.1	7.5	10.2
239-253		2.4	6.4	4.9	5.2
253-267		8.3	8.8	8.2	8.8
267-281		7.3	5.6	0.4*	3.0

H# 15,172
MR 4980
HC 34

TABLE 5 (Continued)

MEAN BODY WEIGHT GAINS OF FEMALE RATS FED FOR TWO YEARS WITH
DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

		MEAN BODY WEIGHT GAINS (g)			
CONCENTRATION	GROUP: (ppm):	II 0	IV 25	VI 500	VIII 2,500
DAYS ON TEST					
281-295		8.5	8.0	11.3	12.3
295-309		8.0	13.5	9.7	8.8
309-323		8.9	12.0	10.3	8.4
323-337		4.4	5.7	7.3	5.5
337-351		13.1	14.3	10.2	9.9
351-365		2.9	4.7	3.6	5.6
365-379		8.0	10.0	11.9	8.1
379-393		12.1	10.8	9.7	4.7*
393-407		6.6	6.8	7.5	9.0
407-421		6.4	5.5	3.8	4.1
421-435		3.4	6.5	2.5	4.0
435-449		2.5	2.4	3.6	2.1
449-463		5.9	3.1	1.7	3.7
463-477		4.1	4.4	4.8	4.7
477-491		0.8	0.3	1.5	1.0
491-505		7.7	10.3	7.4	9.4
505-519		8.0	0.8	3.6	5.9
519-533		-1.6	-5.5	-0.9	-9.6
533-547		-2.5	-2.2	-0.7	0.1
547-561		-2.4	-10.6	0.9	-3.3
561-575		-4.3	-3.9	-7.5	-7.2
575-589		-0.8	-8.9	-2.1	-4.9
589-603		-3.9	-14.9	-3.3	-2.5
603-617		0.1	-10.6	-5.4	2.3
617-631		-3.1	-8.8	1.3	1.3
631-645		-14.8	-16.4	-4.6	-8.6
645-659		-7.2	-13.1	1.2	2.9
659-673		-1.9	0.3	0.2	-0.1
673-687		-5.2	-11.8	-9.6	-1.7
687-701		2.5	-13.8	-6.6	-6.8
701-715		-11.2	-27.7*	-2.1	-6.1
715-729		-7.1	-16.1	-10.2	-3.0
0-182		172.1	175.0	173.5	162.1
182-365		97.9	122.9*	99.2	98.8
365-729		74.3	67.9	59.6	70.1
0-729		341.1	357.2	311.9	330.7

*Different from control at $p < 0.05$ level of significance.

19

H# 15,172
MR 4980
HC 34

TABLE 8 (Continued)

MEAN FOOD EFFICIENCY OF MALE RATS FED FOR TWO YEARS WITH
DIETS THAT CONTAINED 0, 25, 500, OR 2,500 ppm INM-6316

<u>MEAN FOOD EFFICIENCY (g WT GAIN/g FOOD CONSUMED)</u>				
GROUP: CONCENTRATION (ppm):	I 0	III 25	V 500	VII 2,500
DAYS ON TEST				
323-337	0.024	0.017	0.028	0.029
337-351	-0.004	0.003	0.004	0.002
351-365	0.051	0.028	0.040	0.041
365-379	0.022	0.027	0.038	0.032
379-393	0.019	0.020	0.026	0.021
393-407	0.009	0.014	0.019	0.022
407-421	0.014	0.022	0.021	0.017
421-435	0.008	0.015	0.027	0.016
435-449	0.011	-0.010	0.002	0.013
449-463	-0.011	-0.027	0.009	0.009 ^a
463-477	0.002	-0.003	0.014	0.012
477-491	-0.003	-0.009	0.000	0.007
491-505	-0.005	-0.013	0.013	0.002
505-519	-0.015	0.000	0.007	0.014
519-533	-0.025	-0.011	-0.012	-0.022
533-547	-0.012	-0.008	-0.017	-0.001
547-561	-0.023	-0.006	-0.026	-0.012
561-575	-0.018	-0.016	-0.017	-0.031
575-589	-0.052	-0.008	-0.012	-0.039
589-603	-0.033	-0.015	-0.024	-0.046
603-617	-0.013	-0.035	-0.045	-0.046
617-631	-0.007	-0.021	-0.027	-0.011
631-645	-0.050	-0.042	-0.047	-0.052
645-659	-0.069	-0.032	-0.027	-0.048
659-673	-0.059	-0.039	-0.036	-0.043
673-687	-0.079	-0.076	-0.040	-0.064
687-701	-0.079	-0.055	-0.057	-0.080
701-715	-0.058	-0.067	-0.065	-0.087
715-729	-0.074	-0.114	-0.084	-0.058
0-182	0.089	0.090	0.084	0.080
182-365	0.027	0.025	0.027	0.026
365-729	0.000	-0.003	0.005	-0.002
0-729	0.028	0.027	0.029	0.026

^a Due to technical error, diet was discarded for the interval 449-456. This value was calculated based on the low food consumption value given in Table 6.

H-15172
 MK-4980
 HC-34

TABLE II
 SUMMARY OF STATISTICALLY SIGNIFICANT HEMATOLOGIC AND
 CLINICAL CHEMICAL FINDINGS: TWO-YEAR FEEDING

INM-6316
 RAT
 FEMALE

Measurement	3-Month	6-Month	9-Month	12-Month	18-Month	21-Month	24-Month
<u>Hematology</u>							
Ht	-	-	+VIII	-	-	-	+VIII+
MCHC	-	-	-	-	-	-	+VI
Neut	-	-	-	-	-	-	+IV+
<u>Clinical Chemistry (Serum)</u>							
ALP	-	-	-	+VI+	-	-	-
AST	-	-	+IV+	-	-	+IV+, VIII+	+VIII+
CALC	-	-	-	+IV, VI, VIII	-	-	-
CHOL	-	-	-	-	-	-	+VIII+
CREAT	-	-	-	+IV, VIII	-	-	-
TPROT	-	-	-	+VI, VIII	-	+VI	-
ALBMIN	-	-	-	+IV, VI, VIII	-	-	-
Na	-	-	+VI, VIII	+IV, VI, VIII	+IV, VI, VIII	+VIII	+VIII
K	-	-	-	+VIII	-	-	-
<u>Clinical Chemistry (Urine)</u>							
VOL	-	-	-	-	+IV	-	-

+ = Significantly higher than controls by Dunnett or Mann-Whitney U (+) criteria
 - = Significantly lower than controls by Dunnett or Mann-Whitney U (+) criteria

Group Designation and Dose Concentration (ppm)
 IV = Low-Dose (25)
 VI = Intermediate-Dose (500)
 VIII = High-Dose (2500)

2

H-15172
 MK-4980
 IC-34

TABLE I
 SUMMARY OF STATISTICALLY SIGNIFICANT HEMATOLOGIC AND
 CLINICAL CHEMICAL FINDINGS: TWO-YEAR FEEDING

INH-6316
 RAT
 MALE

Measurement	3-Month	6-Month	9-Month	12-Month	18-Month	21-Month	24-Months
<u>Hematology</u>							
PLAT	-	-	-	-	-	-	+III, V, VII
Neut	-	-	+VII+	-	-	-	-
Lymph	-	-	-	-	+V+, VII+	-	-
Alym	-	+V+, VII+	-	-	+V+, VII+	-	-
Mono	-	-	+III+, VII+	-	-	-	-
<u>Clinical Chemistry (Serum)</u>							
ALT	+V+	-	-	-	-	-	-
GLUCO	+III	-	-	+VII	-	-	-
CREAT	-	-	-	-	-	+III+, V+, VII+	-
Na	-	-	+V, VII	+VII	+V+, VII+	-	+III, V, VII
K	-	+V+	-	-	-	-	-
<u>Clinical Chemistry (Urine)</u>							
VOL	-	-	+III	-	-	-	-
OSMOL	+VII	-	+III	-	-	-	-
pH	-	-	+III, V, VII	-	-	-	-
UROBL	-	-	+III, V, VII	-	-	-	-

+ = Significantly higher than controls by Dunnett or Mann-Whitney U (+) criteria
 - = Significantly lower than controls by Dunnett or Mann-Whitney U (+) criteria

Group Designation and Dose Concentration (ppm)

- III - Low-Dose (25)
- V - Intermediate-Dose (500)
- VII - High Dose (2500)

TWO-WAY ANALYSIS OF VARIANCE (ANOVA)
FOR SODIUM CONCENTRATION

A two-way ANOVA for the effects of the compound and time on the serum sodium concentration was calculated. The least significant difference (LSD) was determined to compare dose-group means averaged over time. Both the residual error and the dose/time interaction mean squares were used to calculate a LSD value because of the significant effect of the dose/time interaction.

<u>Error Term</u>	<u>LSD'S</u>	
	<u>Males</u>	<u>Females</u>
Dose/Time	1.26	1.81
Residual	0.78	0.68

DOSE-GROUP MEANS FOR SODIUM AVERAGED OVER TIME

<u>Dose</u>	<u>Males</u>	<u>Females</u>
0 (control)	142.43	142.46
25 ppm	141.99	141.19#
500 ppm	141.26#	139.99#*
2500 ppm	139.99#*	139.12#*

Statistically significant difference at the 5% level using the LSD calculated from the residual error mean square

* Statistically significant difference at the 5% level using the LSD calculated from the dose/time interaction mean square

H# 15,172
MR 4980
HC 34

TABLE XI (Continued)

MEAN RELATIVE ORGAN WEIGHTS (%) OF MALE RATS FED FOR ONE YEAR
WITH DIETS THAT CONTAINED 0, 25, 500, OR 2500 PPM INM-6316

GROUP CONC.	BRAIN		HEART		LIVER	
I CONTROL	0.274(0.000)	0.228(0.000)	3.251(0.000)
III 25 PPM	0.297(0.118)	0.230(0.793)	3.189(0.711)
V 500 PPM	0.303(0.055)	0.245(0.075)	3.392(0.400)
VII 2500 PPM	0.303(0.057)	0.253(0.012)#	3.358(0.524)
TEST - HOMOGENEITY	0.170		0.034		0.592	
TEST - TREND	0.054		0.005		0.325	
BARTLETT'S TEST	0.683		0.784		0.313	
GROUP CONC.	SPLEEN		KIDNEYS		TESTES	
I CONTROL	0.129(0.000)	0.554(0.000)	0.447(0.000)
III 25 PPM	0.122(0.488)	0.560(0.846)	0.459(0.702)
V 500 PPM	0.125(0.656)	0.615(0.046)+	0.492(0.137)
VII 2500 PPM	0.142(0.226)	0.625(0.021)+	0.489(0.171)
TEST - HOMOGENEITY	0.238		0.039		0.352	
TEST - TREND	0.220		0.007		0.101	
BARTLETT'S TEST	0.371		0.025		0.849	

Values in parentheses - P VALUE OF STUDENT T TEST COMPARISON
OF TREATMENT MEAN TO CONTROL MEAN.
+ - SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY LSD
- SIGNIFICANTLY DIFFERENT (P<0.05) FROM CONTROL GROUP BY LSD AND
DUNNETT'S TEST

HOMOGENEITY - P VALUE OF F TEST OF WHETHER GROUP MEANS ARE EQUAL.

TREND - P VALUE OF F TEST OF WHETHER THERE IS DOSE-RELATED
CHANGE IN GROUP MEANS.

BARTLETT'S TEST - P VALUE OF TEST OF HOMOGENEITY OF VARIANCE

24