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SUPPORT: LIFESPAN CHRONIC TOXICITY AND CARCINOGENICITY FEEDING STUDY OF N-FORMYL-4-CHLORO-O-TOLUIDINE IN RATS WITH COVER LETTER DATED 022395			
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N-FORMYL-4-CHLORO-O-TOLUIDINE			

Ciba Plant Protection

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ciba

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February 23, 1995

ORIGINAL

EXPRESS MAIL
RETURN RECEIPT REQUESTED

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FEB 28 AM 11:13

Re: 8EHQ-92-8784; TSCA 8(e) CAP Notice, CGA 72651, Follow-up Submission

Dear Section 8(e) Coordinator:

This letter and the enclosed report contain no Confidential Business Information.

In a telephone conversation with your office on February 14, 1995, it was determined that a report which Ciba's records indicated had submitted as a part of the 8(e) CAP could not be located. The transmittal letter identified by the above referenced Document Control Number was sent on August 19, 1992. In that letter, the CAS Registry Number was incorrectly listed as 87999-30-2. A corrected version of this letter was submitted on September 17, 1993, in which the CAS Registry Number was corrected to 21787-81-5.

We are hereby submitting an original and two copies of the study report (2 volumes, 979 pages) which corresponds to the transmittal letter referenced above, entitled "Lifespan (Chronic Toxicity and Carcinogenicity) Feeding Study in Rats" (Study Number 05688/1).

Please contact the undersigned if you have any questions about this submittal.

Very truly yours,

John A. Stone
Director, Industrial Health



8EHQ-92-8784
SP002 02/28/95

Enclosure

cc: Mr. A. Di Battista



89950000146

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BASLE SWITZERLAND

TOXICOLOGY
GU 2

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N-FORMYL-4-CHLORO-O-TOLUIDINE
LIFESPAN (CHRONIC TOXICITY AND CARCINOGENICITY) FEEDING STUDY
IN RATS

FINAL REPORT

PROJECT NO.: SISS R 05688/1

CIBA - GEIGY
CONFIDENTIAL

JUNE 16, 1980

GSO-D-022465

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Basle/Switzerland
Toxicology
GU 2

C o n t e n t s

	Page
SUMMARY AND ASSESSMENT	
	6
Purpose	9
Procedure	9
METHOD	
	9
Observations and Records	12
Statistical Analysis	12
Clinical Laboratory Investigations	13
RESULTS	
	22
Observations and Records	22
Eye Examination	22
Auditory Perception	22
Clinical Laboratory Investigations	22
<u>Plots and Tables</u>	
Dosage Levels	24
Mean Food Consumption	26
Individual Food Consumption	71
Mean Body Weight	128
Individual Body Weight	182
Mean Food Conversion	282
Physiological Estimate of Haematologic and Urinalysis Values	289
Physiological Estimate of Blood Chemistry Values	297

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37

	Page
Haematology - Means and Individual Values	311
Blood Chemistry - Means and Individual Values	401
Urinalysis - Means and Individual Values	491
Mortality Curves	521
Mean Organ Weights and Ratios	
- after 26 Test Weeks	525
- after 53 Test Weeks	547
- after 105 Test Weeks	563
Individual Organ Weights and Ratios	
- after 26 Test Weeks	529
- after 53 Test Weeks	551
- after 105 Test Weeks	567
PATHOLOGY	
Summary and Assessment	581
Methods	582
Results	582
Bile Duct Pathology and Tumour Profile	584
General Occurrence of Tumours in Rats	595
Macroscopical and Microscopical Findings in Individual Rats	
- 6 Months Interim Sacrifice	596
- 12 Months Interim Sacrifice	616
- Life Span	638

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LIFESPAN (CHRONIC TOXICITY AND CARCINOGENICITY) FEEDING STUDY
IN RATS WITH N-FORMYL-4-CHLORO-O-TOLUIDINE - FINAL REPORT

Material: N-Formyl-4-chloro-o-toluidine
Subject: Lifespan feeding study - Rats
Project No.: Siss R 5688/1
Sponsor: Agricultural Division, Ciba-Geigy Ltd.,
Basle/Switzerland, and
Schering AG., Berlin/Germany

Study Director

Dr. med. vet. K. Sachse
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date: 16. 6. 1980

Responsible for the
animal experimentation

Dr. phil. II, P. Suter
.....
date: 16. 6. 1980

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H. Luetkemeyer, B.Sc.
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date: 19. 6. 1980

Responsible for
the pathology

F. Zak, M.D., Ph.D.
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date: 11. 7. 1980

Reviewed and approved by

Prof. Dr. med. R. Hess
.....
date: 14- 7- 80

5

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Toxicology
GU 2

Reported: June 15, 1980/stu

Archives: Sisseln WST 452
Basle, Rosental 1040

6

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GU 2

SUMMARY AND ASSESSMENT

N-formyl-4-chloro-6-toluidine was administered to rats continuously in the feed over a total period of 105 weeks. Following this period all rats were fed with untreated food up to a survival rate of 20 % per sex and per group. At this time the remaining animals were killed. Groups of 180 rats (90 males, 90 females) received concentrations of 2 ppm (group 2), 20 ppm (group 3), 100 ppm (group 4) and 500 ppm (group 5) in the diet - estimated to be 0.1, 1, 4 and 24 mg/kg/day for the males and 0.1, 1, 5 and 30 mg/kg/day for the females.

An additional group of 180 rats served as the control (group 1) receiving ground diet without substance. Twenty rats (10 males and 10 females) of each group were killed and autopsied after 26 and 53 weeks. After 105 weeks 20 males and 20 females (satellite group for laboratory investigations) of the control and the treated groups were killed and autopsied.

The experiment was carried out under specified pathogen free (SPF) standard laboratory conditions.

The food intake and body weight gain of all treated and control rats were generally comparable during the whole experimental period with the exception of a lower food consumption and body weight gain of the animals of group 5.

The mean food conversion of all treated rats was comparable to the controls.

No clinical symptoms were observed. Eye examinations and hearing tests did not reveal changes which were related to the administration of the substance.

The death rate was comparable between the treated and control rats.

The results of the haematological investigation, blood chemistry data and the urinalysis were generally unremarkable for both treated rats and controls.

At week 4 the haemoglobin concentration was observed to be slightly but significantly below that of the controls in both male and female rats of groups 4 and 5. Similar findings were made in both sexes of group 3 at weeks 13, 26, 52, 76 and 104.

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Slight but significant decreases in the erythrocyte count and packed cell volume, a slight increase in reticulocytes and somewhat higher methaemoglobin values were also seen in both male and female rats of group 5 at weeks 4, 13, 26, 52, 78 and 104.

Organ weights, organ to body weight and organ to brain weight ratios revealed in addition to marked intergroup variations, some statistically significant differences between treated and control animals after 26, 53 and 105 experimental weeks. With the exception of lower body weights of the animals of the highest concentration the findings were not dose related. The most obvious change was a significant increase in absolute and relative liver weights seen in both sexes, but more pronounced in females in the 500 ppm concentration group at test week 105.

Significantly increased incidence of hyperplasia of small biliary ducts was seen in the liver of rats from the highest (500 ppm) concentration group at both 6 and 12 months interim sacrifice. In rats from the same (500 ppm) concentration group which were sacrificed after 2 years of treatment or died after treatment longer than 12 months, markedly increased frequency of multiloculated cholangiogenic biliary cysts in the liver was noted. Both these findings were more pronounced and more frequent in female than in male animals. Incidence of biliary lesions in rats from the 100, 20 and 2 ppm concentration groups was not significantly higher than in the control animals. Hyperplasia of bile-duct tissue is regarded a non-characteristic phenomenon which is independent of parenchymal proliferation. It has been observed to be caused by changes in intrahepatic blood flow, resulting in changes of intravisceral pressure (K. Weinbren and K.V. Chorpade, *Cancer Res.* 22, 881-884, 1962). Alike Burek (J.D. Burek, *Pathology of Aging Rats*, CRC Press, West Palm Beach, 1978) we consider the multilocular biliary cysts, occurring also spontaneously in aging rats, as hyperplasiogenic in nature and not as genuine tumors.

Numerous benign and malignant tumors were observed in both control and treated rats. Frequency and type of the neoplasms occurring in these animals were not influenced by the treatment. Also all other gross and histopathological lesions and changes seen in both control and test animals and described as congenital, degenerative or inflammatory in origin are attributed to the naturally occurring diseases which are common in aged rats of this breeding colony.

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It can be inferred from the observations made during the above study that 20 ppm (approximately 1 mg/kg/day) represents a "no observable effect level" for male and female rats. There was no evidence of carcinogenic potential.

June 16, 1980/stu

GSO-D-022472

Compound: N-formyl-4-chloro-o-toluidine

9

Purpose to determine the chronic toxicity and carcinogenicity of N-formyl-4-chloro-o-toluidine

Procedure According to protocol of 2.9.76 and the amendments of 24.2.77 and 24.7.78

METHOD

Material N-formyl-4-chloro-o-toluidine
Batch No.: AG 11/133 (1-5)
Purity: 99.8 %
Description: white powder
Received: 23.9.76

Project No. Siss R 05688/1

Species RAIf SPF rats (RA 25) bred on the premises.
Equal numbers of males and females.

Mean initial body weight (week -1) 81 - 87 g ♂
78 - 87 g ♀

Initial age approx. 4 weeks

Husbandry The experiment was carried out under specified pathogen free (SPF) standard laboratory conditions. The animals were housed in groups of 5 in macrolon cages type 4 with standardized granulated soft wood bedding (Société Parisienne des sciures Pantin).

The animal room was air conditioned:
temperature: $22 \pm 1^{\circ}\text{C}$
relative humidity: $55 \pm 10\%$
15 - 17 air changes/h
10 hours light/day

Neither insecticides nor chemicals were applied in the animal room with the exception of a disinfectant: Fungitex SB (Prod. Nr. 30071, Ciba-Geigy).

No. of animals/
experimental group 90 males, 90 females
whereas 40 males and 40 females including the animals for laboratory investigations were for interim sacrifices.

GSO-D-022473

Number of Animals / Experimental Group

	MALES					FEMALES				
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 1	Group 2	Group 3	Group 4	Group 5
a)	1- 5	91- 95	181-185	271-275	361-365	451-455	541-545	631-635	721-725	811-815
	6- 10	96-100	186-190	276-280	366-370	456-460	546-550	636-640	726-730	816-820
	11- 15	101-105	191-195	281-285	371-375	461-465	551-555	641-645	731-735	821-825
	16- 20	106-110	196-200	286-290	376-380	466-470	556-560	646-650	736-740	826-830
	21- 25	111-115	201-205	291-295	381-385	471-475	561-565	651-655	741-745	831-835
	26- 30	116-120	206-210	296-300	386-390	476-480	566-570	656-660	746-750	836-840
b)	31- 35	121-125	211-215	301-305	391-395	481-485	571-575	661-665	751-755	841-845
	36- 40	126-130	216-220	306-310	396-400	486-490	576-580	666-670	756-760	846-850
	41- 45	131-135	221-225	311-315	401-405	491-495	581-585	671-675	761-765	851-855
	46- 50	136-140	226-230	316-320	406-410	496-500	586-590	676-680	766-770	856-860
a)	51- 55	141-145	231-235	321-325	411-415	501-505	591-595	681-685	771-775	861-865
	56- 60	146-150	236-240	326-330	416-420	506-510	596-600	686-690	776-780	866-870
d)	61- 65	151-155	241-245	331-335	421-425	511-515	601-605	691-695	781-785	871-875
	66- 70	156-160	246-250	336-340	426-430	516-520	606-610	696-700	786-790	876-880
a)	71- 75	161-165	251-255	341-345	431-435	521-525	611-615	701-705	791-795	881-885
	76- 80	166-170	256-260	346-350	436-440	526-530	616-620	706-710	796-800	886-890
c)	81- 86	171-175	261-265	351-355	441-445	531-535	621-625	711-715	801-805	891-895
	86- 90	176-180	266-270	356-360	446-450	536-540	626-630	716-720	806-810	896-900

- a) Animals for oncogenicity
- b) Animals for laboratory investigations and interim sacrifice after 24 months
- c) Animals for interim sacrifice after 6 months
- d) Animals for interim sacrifice after 12 months

Compound: N-formyl-4-chloro-o-toluidine

Route of Administration oral in the diet

Food pelleted standard diet (Nafag No. 890) ad libitum

Water available at all times

Treatment Mixture to avoid rapid dissipation of the compound the test substance was mixed with the feed, pelleted and immediately deepfrozen. The concentration of the test agent in the food was regularly checked in food samples by chemical analysis*. Food pellets were prepared fresh every two weeks. Aliquots of the pelleted treatment mixture were removed from the freezer every day to be offered to the test animals.

The animals in the control group (group 1) were fed with similarly pelleted food without compound.

Duration of Acclimatization 7 days

Duration of Administration 24 months

Duration of the Study Life time or until 80 % of the animals per group and sex died (the latter refers to the period following the 24 months treatment).

Starting date of Treatment October 11, 1976

Termination date of Treatment October 10, 1978

Termination date of Study

January 12, 1979	-	males of group 2
February 13, 1979	-	males of group 1
February 14, 1979	-	males of group 4
March 5, 1979	-	males of group 5
March 20, 1979	-	males of group 3
March 12, 1979	-	females of group 3
March 19, 1979	-	females of group 5
April 23, 1979	-	females of group 4
May 28, 1979	-	females of group 2
June 5, 1979	-	females of group 1

*) Analysis carried out in the Residue Laboratories of the Agricultural Division of CIBA-GEIGY LTD., Basle/Switzerland

Compound: N-formyl-4-chloro-o-toluidine

Concentration of
active ingredient (nominal) 2, 20, 100, 500 ppm

Observations and Records

Mortality	daily
Symptoms	signs of local and/or systemic toxicity - daily
Tumor Incidence	external signs of tumor formation - weekly
Eye Examination	as well as hearing tests were performed monthly
Body Weight	weekly (first 3 months), monthly thereafter
Food Consumption	once weekly (first 7 months and monthly thereafter) calculated for individual animals
Mean Food Conversion (g food/kg body weight/day)	was calculated according to the following formula: $MFC = \frac{\text{weekly food consumption (g)}}{\text{midweek body weight (g)}} \times \frac{1000}{7}$

Statistical Analysis

for others than Laboratory Investigations:

For each time point and parameter a uni-variate statistical analysis was conducted. Due to the routine manner of the analysis system parameter free methods were applied. Each treated group was compared to the control group in respect of dispersion and displacement* In addition a trend test** was applied considering all groups.

for Laboratory Investigations:

Student's "t" test and the analysis of variance were employed to assess the significance of difference between concentration groups and controls whenever indicated.

*) Y. Lepage, Biometrika (1971) 58: pp. 213-217

**) A. R. Jonckheere, Biometrika (1954) 41: pp.133-143

Compound: N-formyl-4-chloro-o-toluidine

13

Clinical Laboratory Investigations

For comparing some haematological, biochemical and urinalysis values, random samples from untreated male and female RAI (outbred) rats (Sisseln) were taken from different age periods for calculating the Grand Mean, its Standard Deviation and Tolerance Limits. These calculated values are presented on pages 289 to 310.

Haematologic, blood chemistry and urinalysis measurements were carried out by standard methods on 200 randomized rats (20 males, 20 females per group) from the control and four concentration groups at 4, 13, 26, 52, 78 and 104 experimental weeks.

To reduce the biologic variability due to circadian rhythms, blood sampling for haematology and blood chemistry was between the hours of 8.00 and 9.00 a.m. For blood chemistry measurements food was withheld overnight prior to blood removal.

The site of blood removal was the orbital sinus and a micro-haematocrit glass capillary tube was used.

Blood samples from each animal with the respective anticoagulant (EDTA for performing the complete blood count, 3.8 % Sodium Citrate for coagulation testing and Heparin for blood chemistry measurements) were aliquoted into individual vials.

No anaesthesia was used to restrain the animals. All blood collection was by manual restraint only.

Urine for analysis was collected overnight. The individual rats were housed in special metabolism cages. Food and water was withheld during the time of urine collection.

The quantitative assay of all blood parameters was completed within an 8 hr. period under "Quality Control" conditions.

The quality control systems used in haematology, blood chemistry and urinalysis were as follows:

Haematology Reference Control:	CH-60 Normal	(Merz + Dade)
	CH-60 Abnormal	" "
	4C Normal	(Coulter)
	4C Abnormal	" "
	PLACHECK-100	(TOA Medical)

Compound: N-formyl-4-chloro-o-toluidine

Coagulation Reference Control:	CI-TROL-1	(Merz + Dade)
	CI-TROL-2	" "
	CI-TROL-3	" "
	CI-TROL.PTT	" "
	HYLAND 100 %	(Hyland)
	HYLAND 20 %	"
	CONTROL PLASMA	(Behringwerke)
	PATHOPLASMA-1	"
	PATHOPLASMA-2	"

Blood Chemistry Reference Control:	MONI-TROL I	(Merz + Dade)
	MONI-TROL II	" "
	ENZA-TROL	" "
	SERONORM	(Nyegaard)
	LEDER-NORM	(Cyanamid)
	LEDER-TROL	"

Urinalysis Reference Control:	TEK-CHEK	(Ames)
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Parameter Used in Haematologic, Blood Chemistry and Urinalysis Studies

Haematology =====	Method =====	Unit =====
<input checked="" type="checkbox"/> Haemoglobin (Hb):	Cyanmethaemoglobin. Coulter Haemoglobinometer.	g/100 ml
<input checked="" type="checkbox"/> Methaemoglobin (MHb):	Colorimetric. Modified method of Evelyn, K.A. & Malloy, H.T., J. Biol. Chem., 126:655 (1938).	%
<input type="checkbox"/> Carboxyhaemoglobin (Hb-CO):	Photometric Ratio Method.	%
<input checked="" type="checkbox"/> Erythrocytes (RBC):	Coulter Counter Model 2F	X 10 ⁶ Cells/cmm
<input checked="" type="checkbox"/> Packed Cell Volume (PCV):	Clay-Adams Microhaematocrit Centrifuge. Centrifugation by 12,500 r.p.m./3 min.	Vol.-%
<input checked="" type="checkbox"/> Mean Corpuscular Volume (MCV):	Calculated value - $\frac{PCV (\%) \times 10}{RBC (X10^6/mm^3)}$	cu
<input checked="" type="checkbox"/> Mean Corpuscular Haemoglobin (MCH):	Calculated value - $\frac{Hb (g) \times 10}{RBC (X10^6/mm^3)}$	µg

Reticulocytes:

Supravital staining with brilliant cresyl blue.

% Retics/1000 RBC

Inclusion Bodies (I.B.):
(Heinz Bodies)

Supravital staining with neutral red and brilliant green. Examination of 8-10 fields if only a few Heinz Bodies were seen. When numerous 100 cells are counted and the rating made in accordance with the following scheme:

% RBC showing Heinz Bodies

Negative
Occasional
1 - 10 %
11 - 40 %
41 - 75 %
76 - 100 %

Evaluation

0
1
2
3
4
5

Thrombocytes:

Electronic counting with TOA Platelet Counter (Model PL-100)

x 10³ cells/cmm

Prothrombin Time (P):

Quick's one-stage method using Coagulometer of Schnitger and Gross with plasma and Thromboplastin (Merz & Dade).

secs.

Activated Partial
Thromboplastin Time (APTT)

Dade's activated Cephaloplastin method using Coagulometer of Schnitger and Gross. The partial thromboplastin time with kaolin, Proctor, R.R. & Rapaport, S.I., Amer. J. Clin. Path. 36:212 (1961).

secs.

Plasma Viscosity:

Harkness Viscometer. Readings made at 25°C to 0.02 sec. and compared with distilled water (relative viscosity = 1.0). "Rate of Shear" was 660 sec.⁻¹. cp.

Leucocytes:

Total Count:

Differential Count:

Coulter Counter Model ZF

X 10³ cells/cm³

Blood smear stained with the "Ames Hema-Tek Slide Stainer" using "Hema-Tek" Stain-Pak. Meta-Myl. = Metamylocytes
Band = Band Cells
Seg = Segmented Neutrophils
Ly = Lymphocytes
Mo = Monocytes
Eo = Eosinophils
Ba = Basophils
NBL/100 WBC = Normoblast

expressed as a % of total count

Blood Chemistry
=====

Glucose:

LKB Ultralab System. UV-Glucose dehydrogenase method. Banauch, D. et al., Z. klin. Chem. Klin. Biochem. 13, 101-107 (1975). mg/100 ml

Urea (Urea-N):

LKB Ultralab System. Urease method (Berthelot-Reaction). Fawcett, J.K. & Scott, J.E., J. Clin. Path. 13, 156 (1960). mg/100 ml

Total Bilirubin: LKB Ultralab System. Diazotization reaction in the presence of accelerator caffeine-sodium benzoate. Jedrassik, L. & Grof, P., Biochem. Ztschr. 297, 81 (1938). mg/100 ml

Total Protein: LKB Ultralab System. Biuret reaction. Henry, R.J., Clinical Chemistry: Principles and Technics, Harper and Row Publishers, New York, (1964). g/100 ml

Protein Electrophoresis: Agarose gel electrophoresis utilizing Bioware's Cool Pak electrophoretic cell. Evaluation with the Helena Quick Scan and Quick Quant.

Electrolytes:

- Sodium (Na^+): Flame Photometer (EEL 450) mEq/l
- Potassium (K^+): Flame Photometer (EEL 450) mEq/l
- Chloride (Cl^-): Coulometric-Amperometric titration (Buchler-Cotlove Chloridometer). mEq/l

<input checked="" type="checkbox"/>	Glutamate-Oxalacetate Transaminase (GOT):	Eppendorf KEA-5080. UV-absorption with NADH	mU/ml
<input checked="" type="checkbox"/>	Glutamate-Pyruvate Transaminase (GPT):	Eppendorf KEA-5080. UV-absorption with NADH	mU/ml
<input checked="" type="checkbox"/>	Lactate Dehydrogenase (LDH):	Eppendorf KEA-5080. UV-absorption with NADH	mU/ml
<input checked="" type="checkbox"/>	Alkaline Phosphatase (AP):	Eppendorf KEA-5080. Enzymatic hydrolysis of p-nitro-phenylphosphate. O.A. Bessey et al., J. Biol. Chem. 164, 321 (1946).	mU/ml
<input checked="" type="checkbox"/>	γ -Glutamyl Transpeptidase (γ -GT):	Eppendorf KEA-5080. γ -glutamyl-p- nitroanilide + glycylglycine. Szasz, G.: Clin. Chem., 15, 124 (1969).	mU/ml
<input type="checkbox"/>	Acetyl Cholinesterase (Erythrocyte, Plasma and Brain):	Colorimetric: Modified acetylthiocholine DTNB method. Voss, G. and Sachsse, K. Toxicol. Appl. Pharmacol. 16, 764 (1970).	Klett Units

Urinalysis
=====

Urine Volume:

1

Direct measurement.

ml/18 hr.

Specific Gravity:

1

TS Refractometer. (American Optical).

pH:

7

Multistix reagent strips. (Ames Co.).

Protein:

1

Multistix reagent strips. (Ames Co.).

- 0 = negative
- 1 = trace to 30 mg %
- 2 = 30 to 100 mg %
- 3 = 100 to 300 mg %
- 4 = >300 mg %

Glucose:

1

Multistix reagent strips (Ames Co.).

- 0 = negative
- 1 = trace
- 2 = moderate amount
- 3 = large amount

Ketones:

1

Multistix reagent strips. (Ames Co.).

- 0 = negative
- 1 = trace
- 2 = moderate amount
- 3 = large amount

Blood:

Multistix reagent strips. (Ames Co.).

- 0 = negative
- 1 = trace
- 2 = moderate amount
- 3 = large amount

Bilirubin:

Ictotest and Multistix reagent strips. (Ames Co.).

- 0 = negative
- 1 = positive

Urobilinogen:

Multistix reagent strips (Ames Co.).

- 0 = negative
- 1 = positive

Bile Salts:

Pettenkofer and Hay's method.

- 0 = negative
- 1 = positive

Urine Sediment:

Specimen centrifugation at 1000 to 1500 r.p.m. for 5 minutes.

Supravital cytodagnostic staining of sediment employing a modified Sternheimer-Malbin stain.

Microscopy of sediment by 500 x for:

- Erythrocytes
 - Leucocytes
 - Epithelial cells (Squamous & Round)
 - Casts
 - Crystals (Normal & Abnormal)
 - Abnormal constituents
- 0 = negative
 - 1 = occasional
 - 2 = few
 - 3 = moderate amount
 - 4 = large amount

=====

Compound: N-formyl-4-chloro-o-toluidine

22

RESULTS

Observations and Records

Despite of intergroup variations with statistical significance the food intake and body weight gain of all treated and control rats were generally comparable during the whole experimental period with the exception of a lower food consumption and body weight gain of the animals of group 5 (500 ppm).

The mean food conversion of all treated and control rats was comparable.

No clinical symptoms related to treatment were observed during the study.

The death rate was comparable between treated and control rats.

Eye Examination

Eye examination did not reveal any ocular changes which were related to treatment.

Auditory Perception

No loss of hearing ability which was related to treatment was registered.

Clinical Laboratory Investigations

Haematology:

At 4, 13, 26, 52, 78 and 104 experimental weeks, haematological changes apart from the spontaneous age related occurrences were generally unremarkable.

Compound: N-formyl-4-chloro-o-toluidine

In both male and female rats of groups 4 and 5 the haemoglobin concentration was found to be slightly but significantly ($p \leq 0.01$) below that of the controls at week 4. Similar changes were seen in both sexes of group 5 at weeks 13, 26, 52, 78 and 104.

Furthermore, at weeks 4, 13, 26, 52, 78 and 104 slight but significant ($p \leq 0.01$) decreases in the erythrocyte count and packed cell volume were seen in both sexes of group 5.

Associated with these findings was a slight, nevertheless, significant ($p \leq 0.01$) increase in reticulocytes in both sexes of group 5 at weeks 4, 13, 26, 52, 78 and 104.

A slight but significant ($p \leq 0.01$) increase in methaemoglobin formation was also observed in both male and female rats of group 5 at weeks 4, 13, 26, 52, 78 and 104.

Heinz bodies generally associated with mehaemoglobin formation were not observed.

Blood Chemistry:

The results of the blood chemistry analysis at 4, 13, 26, 52, 78 and 104 weeks were unremarkable for both treated rats and controls.

Urinalysis:

The findings in the urine apart from spontaneous age related occurrences were generally unremarkable.

Most rats revealed some degree of physiological proteinuria including those of the control group. This is considered normal in laboratory rats.