

**FYI-0401-1408**

**46740**

**TSCA HEALTH & SAFETY STUDY COVER SHEET - revised 6/25/96**

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<b>2.1 SUMMARY/ABSTRACT ATTACHED</b> (may be required for 8(e); optional for §4, 8(d) & FYI) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	<b>2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID</b>	<b>2.3 FOR EPA USE ONLY</b>
<b>3.0 CHEMICAL/TEST SUBSTANCE IDENTITY</b> <input type="checkbox"/> Contains CBI Reported Chemical Name (specify name/structure if other than CAS name): <u>1-Tetradecanium, N,N-dimethyl-N-tetradecyl-, hexa-, mu.-oxotetra-, mu. 3-oxodi-, mu. 5-oxotetradecaooxooctamolydate (4-)</u> CAS# <u>1.0342-25-3</u> Purity _____ % <input checked="" type="checkbox"/> Single Ingredient <input type="checkbox"/> Commercial/Tech Grade <input type="checkbox"/> Mixture Trade Name: _____ Common Name: _____ CAS Number: _____ NAME: _____ % WEIGHT: _____ Other chemical(s) present in tested mixture: _____ <input type="checkbox"/> continuation sheet attached		
<b>4.0 REPORT/STUDY TITLE</b> <input type="checkbox"/> Contains CBI <u>TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat</u> <input type="checkbox"/> continuation sheet attached		
<b>5.1 STUDY/TSCATS INDEXING TERMS</b> [CHECK ONE] HEALTH EFFECTS (HE): <input checked="" type="checkbox"/> ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____		
<b>5.2 STUDY/TSCATS INDEXING TERMS</b> (see instructions for 4 digit codes) STUDY TYPE: _____ SUBJECT ORGANISM (HE, HE only): _____ ROUTE OF EXPOSURE (HE only): <u>INHL</u> VEHICLE OF EXPOSURE (HE only): _____ Other: _____ Other: _____ Other: _____ Other: _____		
<b>6.0 REPORT/STUDY INFORMATION</b> <input type="checkbox"/> Contains CBI <input type="checkbox"/> Study is GLP Laboratory: <u>Covance Laboratories Ltd.</u> Report/Study Date: <u>Jan 91</u> Source of Data/Study Sponsor (if different than submitter): _____ Number of pages: <u>58</u> <input type="checkbox"/> continuation sheet attached		
<b>7.0 SUBMITTER INFORMATION</b> <input type="checkbox"/> Contains CBI Submitter: _____ Title: _____ Phone: (914) <u>422-0888</u> Company Name: <u>Hodogaya Chemical (U.S.A.) Inc.</u> Company Address: <u>123 Main Street</u> <u>White Plains, NY 10601</u> Submitter Address (if different): _____ Technical Contact: <u>Naomichi Nakashima</u> Phone: (914) <u>422-0888</u> <input type="checkbox"/> continuation sheet attached		
<b>8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS</b> <input type="checkbox"/> Contains CBI <input type="checkbox"/> continuation sheet attached		

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Submitter Signature: Naomichi Nakashima

Date: 4/6/01

# Final Report

**Study Title** TP-415 Toner: Single Exposure (Nose-only)  
Toxicity Study in the Rat

**Data Requirement** Environmental Protection Agency (USA)  
Prevention, Pesticides and Toxic Substances  
(7101) EPA 712-C-96-193 August 1998. Health  
Effects Test Guidelines OPPTS 870.1300 Acute  
Inhalation Toxicity

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**Covance Study Number** 558/11

**Covance Report Number** 558/11-D6154

**Report Issued** January 2001

**Page Number** 1 of 58

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**STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS**

**TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat**

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Sections § 10(d)(1)(A), (B) or (C).

Company \_\_\_\_\_

Company Agent: \_\_\_\_\_ Date: \_\_\_\_\_

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These data are the property of Hodogaya Chemical (USA), INC. and as such are considered to be confidential for all purposes other than compliance with FIFRA § 10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any statute or in any other country.

**GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT**

**TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat**

The study was conducted in compliance with:

United Kingdom Statutory Instrument 1999 No. 3106, The Good Laboratory Practice Regulations 1999.

OECD Principles on Good Laboratory Practice (revised 1997, issued Jan 1998) ENV/MC/CHEM(98)17.

These international standards are acceptable to the United States Environmental Protection Agency 40 CFR Part 160.

N M Shepherd  
N M Shepherd  
Study Director  
Covance Laboratories Ltd

3 Jan 2001  
Date

\_\_\_\_\_  
Name  
Sponsor  
Department or Company

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name  
Submitter  
Department or Company

\_\_\_\_\_  
Date

**FLAGGING STATEMENTS**

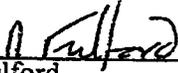
**TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat**

**QUALITY ASSURANCE STATEMENT****TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat**

The study described in this report was subject to audit by the independent Quality Assurance Department as indicated below. The findings of each audit were reported to the Study Director and management as prescribed by Standard Operating Procedures.

The report audit was designed to confirm that the methods described and results incorporated in the report accurately reflect the raw data produced during the study.

<b>Inspection programme</b>	<b>Inspection date</b>	<b>Report date</b>
Protocol review	20 March 2000	20 March 2000
Inhalation exposure	18 May 2000	18 May 2000
Data review	October 2000	13 October 2000
Draft study report	October 2000	13 October 2000

  
 \_\_\_\_\_  
 A Fulford  
 Section Head Quality Assurance  
 Covance Laboratories Ltd.

3 January 2001  
 Date

**RESPONSIBLE SCIENTISTS' STATEMENT**

**TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat**

I, the undersigned, hereby declare that the work described in this report was performed under my supervision, and that the report provides a true and accurate record of the results obtained.

  
\_\_\_\_\_  
N M Shepherd BSc  
Study Director  
Covance Laboratories Ltd

3 June 2001  
Date

I, the undersigned, hereby declare that I have reviewed this report in conjunction with the Study Director and that the interpretation and presentation of the data in the report are consistent with the results obtained.

  
\_\_\_\_\_  
J C Norris PhD DABT  
Section Manager - Inhalation Toxicology  
Covance Laboratories Ltd

27 June 2001  
Date

**RESPONSIBLE PERSONNEL**

**TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat**

In addition the following staff were responsible for key elements of the study:

Deputy Study Director	A C Gibbs
Head of Pathology	J Glaister
Head of Statistics	C Gardner
Inhalation Chemistry	B Canham
Animal house supervisor	J Gladstone
Animal health and welfare	A Basford
Histology	S Brogden
Necropsy	I Wilkins
Head of Information Technology	N Darwent
Head of Quality Assurance	S White#

# With effect from 11 May 2000 the responsibility for Quality Assurance at Covance transferred from S White, Head of Quality Assurance to D Kirkland, Vice President of Consultancy and Regulatory Services.

**ARCHIVE STATEMENT****TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat**

All primary data or authenticated copies thereof, specimens and the final report will be retained in the Covance archives for ten years after submission of the final report. At this time the Sponsor will be contacted to determine whether data should be returned, retained or destroyed on their behalf. The Sponsor will be notified of the financial implications of each of these options at that time.

Specimens requiring storage, deep frozen, are specifically excluded from the above. These will be retained for as long as the quality of the material permits evaluation but for no longer than three months after submission of the final report. The Sponsor will be notified of the intent to destroy samples and any financial implications before specimens are destroyed on their behalf.

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## SUMMARY

The objective of the study was to determine the toxicity of the test article, TP-415 Toner, following a 4-hour inhalation exposure (nose-only).

One group of ten rats (five males and five females) of the Cr:CD<sup>®</sup> (SD)IGSBR strain was exposed to the following chamber concentrations by nose-only inhalation over a period of four hours:

Group number	Group description	Oxygen concentration (%)	Nominal concentration (mg/L)	Chamber concentration (mg/L)	Particle size# (µm)
1	High	>19	17.9	2.14	7.79

# Median value for mass median aerodynamic diameter.

Exposure was followed by an observation period of 14 days.

The test article was used as supplied. The chamber temperature recorded for the treated group ranged between 19 and 20°C with relative humidity between 45 and 47%. The chamber air flow rate was 16 L/min throughout the exposure, with 24 air changes/hour.

There were no deaths, effects on body weight, clinical observations or necropsy observations attributable to exposure to the test article during the course of the study.

In conclusion, a single exposure to the test article, TP-415 Toner, at an atmosphere concentration of 2.14 mg/L for 4 hours was well tolerated and did not result in deaths. As no deaths occurred, it can be concluded that the 4-hour acute medium lethal concentration (LC<sub>50</sub>) is above 2.14 mg/L. Under EPA OPPTS 870.1000 guidelines, the test article is classified as Category IV.

## INTRODUCTION

The objective of the study was to determine the toxicity of the test article, TP-415 Toner, following a 4-hour inhalation exposure (nose-only).

The test article was assigned a toxicity category according to toxicity assessment criteria (see Appendix 1). This determination of toxicity class minimises the animal usage.

The inhalation route of administration was chosen because it is a possible route of human exposure.

The rat was selected because it is a rodent species recommended by various regulatory authorities. Background data are available.

### Study dates

Protocol signed by Study Director:	17 March 2000
Animals on site & experimental start date:	18 April 2000
First treatment:	18 May 2000
Study termination:	1 June 2000
Experimental completion date:	1 June 2000

The study completion date is the date the final report is signed by the Study Director.

**PROTOCOL ADHERENCE**

The study was conducted in accordance with the agreed definitive protocol and one protocol amendment. There were no major deviations from the protocol. Minor deviations, which did not affect the integrity or outcome of the study, are presented in the report.

**TEST ARTICLE**

The test article, a black powder (toner) including 3.0% of TP-415, was identified as TP-415 Toner. The test article was received at Covance as follows:

Test Article	Covance Lot Number	Lot Number	Quantity supplied (g)	Expiry Date	Date of receipt at Covance
TP-415 Toner	1	001	1350	31 August 2000	30 March 2000

When not in use the test article was stored at room temperature in the dark.

A certificate of analysis for the test article was provided by the Sponsor.

**EXPERIMENTAL DESIGN**

**Regulatory test guidelines**

This study was designed to meet the known requirements of the Environmental Protection Agency (USA) Prevention, Pesticides and Toxic Substances (7101) EPA 712-C-96-193 August 1998. Health Effects Test Guidelines OPPTS 870.1300 Acute Inhalation Toxicity.

**Test article administration**

The test article was administered by nose-only inhalation in a single 4-hour exposure in a chamber of 40 L internal volume for the exposure.

**Limit test**

This was performed at a concentration of 2.14 mg/L.

One group of ten rats (five males and five females) was exposed as follows:

Group number	Group description	Nominal concentration (mg/L)	Chamber concentration (mg/L)	Animals	
				Male	Female
1	High	17.9	2.14	5	5

The day of exposure was followed by a 14-day observation period.

**TEST ARTICLE ATMOSPHERE GENERATION**

**Development of the test atmosphere**

Atmosphere development was conducted using the test article as supplied. Data collected during atmosphere development are retained in the study records but not reported.

**Generation of the test atmosphere**

An Auger dust feed generator located immediately above the chamber was used to produce the atmosphere of test article. A schematic diagram of the continuous flow system used is shown in Appendix 1.

**ATMOSPHERE CONTROL**

**Exposure chamber temperature and relative humidity**

The temperature and relative humidity in the chamber were monitored continuously and recorded twice hourly.

**Exposure chamber air flow**

The air flow through the exposure chamber was monitored continuously and recorded twice hourly.

**Exposure chamber oxygen concentration**

The oxygen concentration in the exposure chamber was monitored continuously and recorded twice hourly.

**Nominal concentration**

The test article was weighed before and after exposure to determine the amount utilised during the exposure period.

**Exposure concentration**

The actual concentration in the exposure chamber was measured gravimetrically approximately twice hourly during the exposure period.

**Particle size**

The particle size of the atmosphere was measured prior to exposures, and then hourly for each test group using gravimetric methodology. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated for each occasion.

**TEST SYSTEM****Species, strain and supplier**

A sufficient number of rats of the CrI:CD<sup>0</sup>(SD)IGSBR strain were obtained from Charles River (UK) Ltd, Margate, to provide 5 healthy animals of each sex.

**Specification**

The animals were ordered in the weight range 151 to 175 g and were about 5 weeks old on arrival. They were held in stock under standard conditions of environment and husbandry until allocated to this study. As the animals were held in stock prior to the start of the study, the actual animal order did not reflect the protocol requirements. Pre-exposure (after allocation) their body weight was within  $\pm 20\%$  of the overall mean for each sex. They were approximately 9 weeks old at start of treatment.

**Environment and husbandry**

The animals were held in stock in a single room for two weeks before transfer to the study room. After transfer to the study, the animals were housed in a single room, air-conditioned to provide a minimum of 15 air changes/hour and routinely maintained at a temperature of 19 to 25°C and a relative humidity of 40 to 70%. Fluorescent lighting was controlled automatically to give a cycle of 12 hours light (0600 to 1800 h) and 12 hours darkness.

**Housing**

The animals were housed in groups of five in stainless steel wire mesh cages of size 55 x 34 x 20 cm, floor area 1870 cm<sup>2</sup>.

**Diet and water**

Throughout the study, except during exposure, the animals had access *ad libitum* to SQC Rat and Mouse Maintenance Diet No 1, Expanded, (Special Diets Services Ltd. Witham). Each batch of diet was analysed for specific constituents and contaminants.

A certificate of analysis for the batch of diet used on this study is presented in Appendix 5.

Mains drinking water was available *ad libitum*, except during the exposure period, from water bottles attached to the cages.

The diet and water were considered not to have contained any contaminant at a level which might have affected the integrity or outcome of the study.

**PRE-EXPERIMENTAL OBSERVATIONS****Acclimatisation and health procedures**

All animals were given a clinical inspection for ill health on arrival. They were held in stock and acclimatised to study conditions before being allocated to the study. A veterinary inspection was performed before the start of exposure to ensure their suitability for the study.

**Allocation to treatment group**

Animals were assigned arbitrarily, by sex, to the test group during the acclimatisation period.

**Identification of the test system**

After allocation to treatment group each animal was permanently numbered by indelible ink on the tail as follows:

Group number	Colour code	Animal identification numbers	
		Male	Female
1	Pink	1 - 5	6 - 10

Cages were appropriately identified with study information including study number and animal numbers.

**EXPERIMENTAL OBSERVATIONS****Clinical signs**

Animals were observed for signs of ill health or overt toxicity. Animals were observed approximately hourly during the exposure period and for the remainder of the exposure day. They were observed daily during the remainder of the study. An individual record was maintained on the clinical condition of each animal.

**Morbidity and mortality**

All animals were examined at the beginning and the end of the working day to ensure the animals were in good health.

**Body weight**

Individual body weights were recorded immediately before and after exposure on Day 1, and on Days 2, 8 and 15 of the study and before necropsy.

---

**TERMINAL PROCEDURES**

The following procedures were applied to all animals killed at the end of the study:

**Necropsy**

At the terminal kill, the animals were given an intraperitoneal injection of sodium pentobarbitone. Following exsanguination, a full macroscopic examination was made under the general supervision of a pathologist and all lesions were recorded. The nasal cavity and respiratory tract were examined and any irritation assessed.

**Histopathology**

Samples of all gross lesions were fixed in the appropriate fixative and retained without further processing.

**DATA EVALUATION**

Any signs of toxicity and mode of death were assessed. Data were processed, where appropriate, to give group mean values and standard deviations.

No further statistical analyses were performed.

## RESULTS

### Atmosphere control (Table 1)

#### Exposure chamber temperature and relative humidity

The chamber temperature recorded for the treated group ranged between 19 and 20°C and the relative humidity ranged between 45 and 47%.

#### Exposure chamber air flow

The flow rate was 16 L/min throughout the exposure, and there were approximately 24 air changes/hour.

#### Exposure chamber oxygen concentration

The oxygen concentration was between 20.5 and 20.9%.

These values were considered to be satisfactory. The recorded temperature of 19°C, was considered not to have affected the interpretation or outcome of the study.

### Measured exposure chamber atmosphere concentrations (Table 1)

The mean concentration of the generated atmosphere was 2.14 mg/L with a standard deviation of 0.56 mg/L and individual values in the range of 1.27 to 3.11 mg/L. The corresponding nominal concentration was 17.9 mg/L. The efficiency of generation was 12%.

### Exposure chamber particle size analysis (Table 1)

The median value for the mass median aerodynamic diameter (MMAD) of the particles in the atmosphere for the various groups was 7.79 µm. The corresponding value for the geometric standard deviations was 3.28. Sampling of atmospheres generated during atmosphere development indicated that the particle size was routinely in the range of approximately 5 to 8 µm with two values of 1.37 and 2.94 µm. Given the number of larger MMAD values, the generation of these latter two values was considered random and consequently demonstrated that the atmosphere could not be controlled consistently at these lower MMAD values. Since the particle size obtained during the animal exposure was the smallest practically possible, it was considered that the animals were adequately exposed to the test article.

**Mortality**

There were no deaths.

**Clinical observations (Table 2)**

The observations noted on the day of exposure were wet and stained fur. Of these findings, only stained fur persisted until Day 3. There were no clinical observations for all the animals from Day 4 until the end of the observation period.

**Body weight (Figure 1, Table 3, Appendix 2)**

Over the observation period, all animals gained weight, following a brief expected weight loss attributed to the exposure and associated restraint procedure.

**Necropsy (Appendix 3)**

At necropsy there were no observations suggestive of an effect of treatment.

**Acute median lethal concentration**

As there was no mortality, the acute median lethal concentration and its fiducial limits were not calculable. However, it can be concluded that the 4-hour acute median lethal concentration (LC<sub>50</sub>) is greater than 2.14 mg/L.

**Toxicity assessment classification (Appendix 1)**

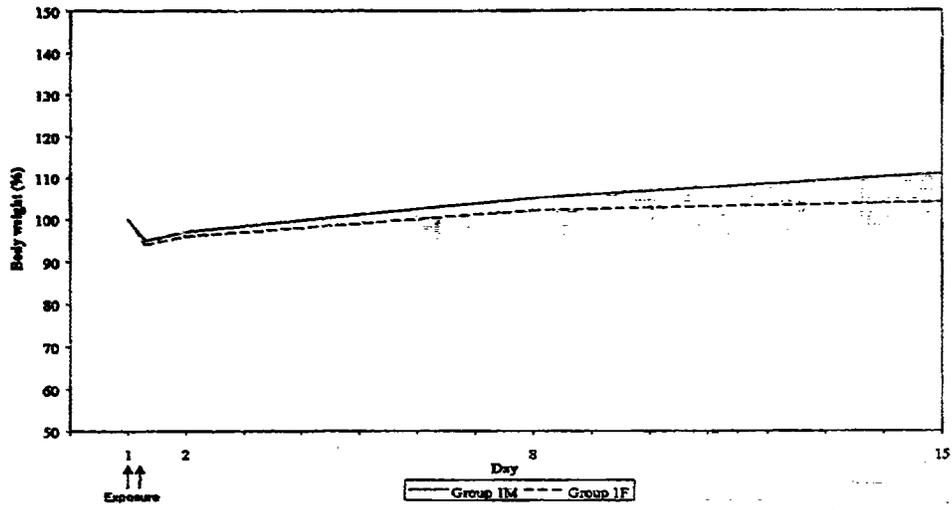
Under EPA OPPTS 870.1000 guidelines, the test article is classified as Category IV.

### CONCLUSION

A single exposure to the test article, TP-415 Toner, at an atmosphere concentration of 2.14 mg/L for 4 hours was well tolerated and did not result in deaths. As no deaths occurred, it can be concluded that the 4-hour acute medium lethal concentration (LC<sub>50</sub>) is above 2.14 mg/L. Under EPA OPPTS 870.1000 guidelines, the test article is classified as Category IV.

**FIGURE**

**Figure 1**  
**Group mean body weight as a percentage of pre-exposure value**



**TABLES**

**Table 1**  
**Individual and group mean inhalation data**

Group 1							
Time point (min into exposure)	Chamber conditions				Air flow (L/min)	Particle size	
	Temperature (°C)	Humidity (%)	Oxygen (%v/v)	Chamber concentration (mg/L)		MMAD (µm)	GSD
0	19	45	20.5	16			
20					1.73		
30	20	47	20.8	16			
36						9.88	3.35
50					2.22		
60	20	47	20.8	16			
80					2.24		
90	20	46	20.8	16			
99						8.15	3.20
110					1.93		
120	20	46	20.7	16			
140					1.27		
150	20	46	20.9	16	2.83		
161						7.42	7.44
170					2.17		
180	20	46	20.9	16			
200					3.11		
210	20	45	20.6	16			
216						5.67	2.84
220					1.80		
240	19	45	20.5	16			
Mean	20	46	20.7	16	2.14	7.79#	3.28#
SD	0	1	0.2	0	0.56		

Nominal concentration (mg/L) = 17.9

MMAD = mass median aerodynamic diameter

GSD = geometric standard deviation

# median value

Particle size data obtained during atmosphere development:

MMAD	GSD
2.94	6.55
5.60	8.63
6.15	2.91
1.37	9.24
5.52	3.71
7.51	4.24

**Table 2**  
**Group summary of clinical signs**

Group and sex	Signs of reaction	Number showing sign during day of exposure	Number showing sign on day of observation:							
			2	3	4	5	6	7	8	
1M	Normal				5	5	5	5	5	
	Fur - staining, body	5								
	Fur - staining, head	5	5	5						
	Fur - wet, body	5								
	Fur - wet, head	5								
	Tail - staining		5							
1F	Normal				5	5	5	5	5	
	Fur - staining, body	5	1							
	Fur - staining, head	5	5	5						
	Fur - wet, body	5								
	Fur - wet, head	5								
	Tail - staining		5							

Group And sex	Signs of reaction	Number showing sign on day of observation:							
		9	10	11	12	13	14	15	
1M	Normal	5	5	5	5	5	5	5	
1F	Normal	5	5	5	5	5	5	5	

**Table 3**  
**Group mean body weight as a percentage of pre-exposure value**

Group and sex		% Pre-exposure on Day:				
		1 Pre-exposure	1 Post-exposure	2	8	15
1M	Mean	100	95	97	105	111
	SD	0	1	1	1	2
1F	Mean	100	94	96	102	104
	SD	0	1	2	1	3

**APPENDICES**

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## Appendix 1 Inhalation procedures

### Generation of Test Atmosphere

An Auger dust feed generator located immediately above the chamber and supplied with compressed air was used to produce the atmosphere of test article.

The atmosphere was introduced into the top of a cylindrical aluminium chamber of approximately 40L internal volume.

The test atmosphere was filtered using a cartridge particulate filter, exhausted to the outside of the building and vented.

## ATMOSPHERE CONTROL

### Exposure chamber temperature and relative humidity

The temperature and relative humidity inside the exposure chamber were monitored using a digital thermometer with a remote probe located inside the chamber and a hair hygrometer located in the exhaust duct of the chamber.

### Chamber air flow

Chamber air flow was monitored continuously using flow meters throughout the exposure period.

### Exposure chamber oxygen concentration

The oxygen concentration inside the chamber was monitored using an oxygen monitor incorporating a remote sensor.

### Nominal concentration

Nominal concentration is defined as the amount of test article released per minute from the generator divided by the airflow per minute passing through the exposure system. The nominal concentration of the test article in the exposure chamber was calculated as shown:

$$\text{Nominal concentration (mg/L)} = \frac{\text{weight of test article used (g)}}{\text{chamber air flow (L/min)} \times \text{duration (min)}} \times [10^3]$$

Where  $[10^3]$  is the conversion factor, changing g to mg

#### **Exposure concentration**

Samples were obtained during the exposure period. The concentration of the test article was determined gravimetrically. The atmosphere was sampled by drawing a known volume through a glass fibre open face filter positioned at a site representative of that occupied by the external nares of the experimental animals. The filter was weighed before and after sampling and the measured concentration of the test atmosphere was calculated as follows:

$$\text{Gravimetric concentration (mg/L)} = \frac{\text{total weight gain (g)}}{\text{sampling air flow (L/min)} \times \text{duration (min)}} \times [10^3]$$

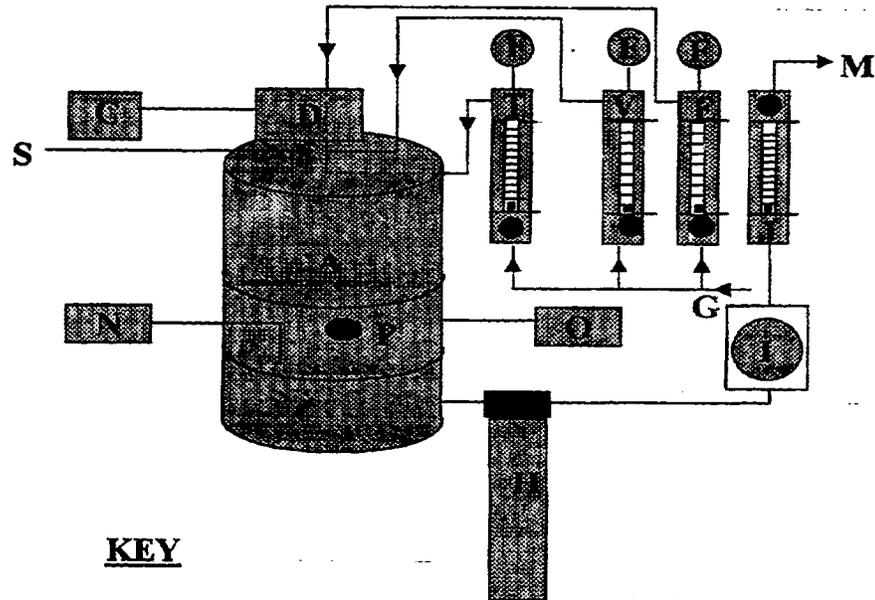
Where  $[10^3]$  is the conversion factor, changing g to mg

#### **Exposure chamber particle size analysis**

The particle size was determined using an Andersen 298 Marple Cascade Impactor, with nine separation stages corresponding to cut off limits of 0.52, 0.93, 1.55, 3.50, 6.00, 9.80, 14.80, 21.30 and 100  $\mu\text{m}$ . The samples were obtained hourly over a period of one minute at each exposure period.

The cumulative percentage by weight of test article collected at each successive stage was plotted by computer as a probability value against the logarithmic value of the upper class limit of that stage. Weights collected at stages corresponding to mass median aerodynamic diameters of 21.30 and 100  $\mu\text{m}$  were combined and the stage re-identified. The point at which the cumulative distribution line crossed the 50 percentile was the estimate of the mass median aerodynamic diameter (MMAD). The Geometric Standard Deviation was also calculated.

**Figure**  
**Schematic representation of exposure system**



**KEY**

- A - 40L volume ADG nose-only exposure chamber
- C - Auger dust feed motor control
- D - Auger dust feed
- E - Dust carrier air supply flow meter
- F - Pressure gauge
- G - Breathing quality air supply
- H - 20" long, 3.0µm pore size, particulate filter
- I - Humidity meter housed in polycarbonate cylinder
- J - Chamber exhaust air flow meter
- M - Exhaust source
- N - Temperature sensor and digital display
- O - Oxygen meter sensor and digital display
- P - Chamber atmosphere sampling port
- R - Pressure gauge
- S - Venturi
- T - Cyclone air supply flow meter
- V - Venturi air supply flow meter

**Toxicity assessment criteria**

The data obtained in the single dose inhalation study can be compared with the proposed toxicity classification below:

Environmental Protection Agency (USA), Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-98-189 August 1998, Health Effects Test Guidelines OPPTS 870.1000, Acute Inhalation Toxicity Testing – Background

Toxicity category by inhalation	LC <sub>50</sub> (mg/L)
I	≤ 0.05
II	> 0.05 - 0.5
III	> 0.5 - 2.0
IV	> 2.0

**Appendix 2**  
**Individual and group mean body weights**

Group and sex	Animal number	Body weight (g) on Day:				
		1	2	8	15	
		Pre-exposure	Post-exposure			
1M	1	386	362	373	408	435
	2	342	328	333	357	377
	3	344	326	334	362	381
	4	320	305	309	334	359
	5	351	330	336	366	381
	Mean	349	330	337	365	367
	SD	24	20	23	27	29
1F	6	263	248	259	269	287
	7	263	247	255	269	277
	8	229	213	222	229	233
	9	235	222	223	242	243
	10	246	231	233	248	252
	Mean	247	232	238	251	258
	SD	16	15	18	17	23

**Appendix 3**  
**Individual necropsy data**

Group 1										
Animal number and sex	1M	2M	3M	4M	5M	6F	7F	8F	9F	10F
NECROPSY										
Animal not remarkable (NR)	NR	NR	NR	NR		NR	NR	NR	NR	NR
Lung - red focus: post caval lobe										P
- red focus: right middle lobe										P

P = present

Appendix 4  
Sponsor's certificate of test article analysis



To whom it may concern :

CERTIFICATION OF ANALYSIS

November 30, 2000

We hereby certify that following commodity have been duly inspected by us and found to be in full conformity with our standard quality.

Sample Name	TP-415 TONER
Ex-Factory Date	March 20, 2000
Lot No.	001
Quantity	1.36 Kg

ITEM	TEST RESULTS
Appearance	Black powder
TP-415 Content Matter (%)	3.0
Acrylic Polymer (%)	92.0
Carbon Black (%)	5.0
Particle Size ( $\mu$ m)	10.0
TG ( $^{\circ}$ C)	63.0
Melting Point ( $^{\circ}$ C)	114.0
Water Solubility (%)	None



保土谷化学工業株式会社  
HODOGAYA CHEMICAL CO., LTD.

〒212-8588 川崎市幸区堀川町66-2  
66-2, HORIKAWA-CHO, SAIWAI-KU, KAWASAKI-SHI, 212-8588, JAPAN

HODOGAYA CHEMICAL CO., LTD

*Yusaku Okada*  
General Manager  
Imaging Materials Div.

Appendix 5  
Certificate of diet analysis



Special Quality Control Certificate of Analysis

PRODUCT: RMI (E) SQC  
PREMIX BATCH NO: 933

BATCH NO: 6406  
DATE OF MANUFACTURE: 15-DEC-99

Nutrient	Found Analysis		Contaminant	Found Analysis	Limit of Detection
Moisture	10.9	%	Fluoride	6 mg/kg	1.0 mg/kg
Crude Fat	3.1	%	Nitrate as NaNO3	37 mg/kg	1.0 mg/kg
Crude Protein	13.3	%	Nitrite as NaNO2	1.9 mg/kg	1.0 mg/kg
Crude Fibre	5.2	%	Lead	0.33 mg/kg	0.25 mg/kg
Ash	4.7	%	Arsenic	Non Detected mg/kg	0.2 mg/kg
Calcium	0.74	%	Cadmium	Non Detected mg/kg	0.05 mg/kg
Phosphorus	0.56	%	Mercury	Non Detected mg/kg	0.01 mg/kg
Sodium	0.27	%	Selenium	0.07 mg/kg	0.05 mg/kg
Chloride	0.43	%			
Potassium	0.76	%			
Magnesium	0.18	%	Total Aflatoxins	Non Detected mcg/kg	1 mcg/kg each of B1, B2, G1, G2
Iron	141	mg/kg			
Copper	14	mg/kg	Total P.C.B	Non Detected mcg/kg	10.0 mcg/kg
Manganese	65	mg/kg	Total D.D.T	Non Detected mcg/kg	10.0 mcg/kg
Zinc	25	mg/kg	Dieldrin	Non Detected mcg/kg	10.0 mcg/kg
			Lindane	Non Detected mcg/kg	10.0 mcg/kg
			Heptachlor	Non Detected mcg/kg	10.0 mcg/kg
			Malathion	Non Detected mcg/kg	20.0 mcg/kg
Vitamin A	4.9	iu/g	Total Viable Organisms x 1000	Non Detected per gram	1000/g
Vitamin E	48	mg/kg			
Vitamin C		mg/kg	Mesophilic Spores x 100	9 per gram	100/g
			Salmonellae Species	Non Detected per gram	Absent in 20 gram
			Enterobacteriaceae	Non Detected per gram	Absent in 20 gram
			Escherichia Coli	Non Detected per gram	Absent in 20 gram
			Fungal Units	Non Detected per gram	Absent in 20 gram
			Antibiotic Activity	Non Detected	

Signed *R3 f [Signature]*  
Dated *12/11/2000*



SHOW NUTRITION

**Appendix G**  
**Study protocol****Definitive Protocol**

<b>Study Title</b>	TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat
<b>Data Requirement</b>	Environmental Protection Agency (USA) Prevention, Pesticides and Toxic Substances (7101) EPA 712-C-96-193 August 1998. Health Effects Test Guidelines OPPTS 870.1300 Acute Inhalation Toxicity
<b>Study Director</b>	N M Shepherd
<b>Sponsor</b>	HODOGAYA CHEMICAL (USA), INC. 123 Main Street White Plains N.Y. 10601 USA
<b>Study Monitor</b>	Mr K Kashima Hodogaya Chemical Co., Ltd. 66-2 Horikawa-cho Saiwai-ku Kawasaki-shi 212-8588 Japan
<b>Test Facility</b>	Covance Laboratories Ltd Otley Road, Harrogate North Yorkshire HG3 1PY ENGLAND
<b>Covance Study Number</b>	558/11
<b>Page Number</b>	1 of 19

#### INTRODUCTION

The objective of the study is to determine the toxicity of the test article, TP-415 Toner, following a 4-hour inhalation exposure (nose-only).

The test article will be assigned a toxicity category according to toxicity assessment criteria (see Appendix 4). This determination of toxicity class minimises the animal usage. The data obtained may not permit computation of the median lethal concentration but where possible this will be estimated.

The route of administration by inhalation has been chosen because it is a possible route of human exposure.

The rat has been selected because it is a rodent species recommended by various regulatory authorities. Background data are available.

### TEST ARTICLE

The test article is identified as TP-415 Toner.

The Sponsor will provide as much information as possible on the physical appearance, known hazardous properties, purity, stability and a date of expiry. A sample for archive will be the responsibility of the Sponsor.

When not in use, the test article will be stored in a sealed container, at room temperature in the dark.

Any vehicle control used will be recorded in the study records.

After the issue of the final report of the study, any remaining test article will be disposed of according to the Sponsor's instructions using standard procedures, e.g. return to the Sponsor or incineration. Costs associated with disposal may incur an additional charge, but this would be discussed with the Sponsor prior to the test article disposal.

### EXPERIMENTAL DESIGN

#### Regulatory test guidelines

This protocol is designed to meet the known requirements of the Environmental Protection Agency (USA) Prevention, Pesticides and Toxic Substances (7101) EPA 712-C-96-193 August 1998. Health Effects Test Guidelines OPPTS 870.1300 Acute Inhalation Toxicity.

#### Exposure to the test article

The test article will be administered as a single 4-hour exposure via inhalation (nose-only) in a chamber having a volume of approximately 0.040 m<sup>3</sup> and being constructed of aluminium and glass. A schematic diagram of the exposure system is in Appendix 3.

**Exposure level**

**Limit study** - The exposure concentration will be approximately 2 mg/L for 5 males and 5 females exposed simultaneously for 4 hours. Animals will be observed for 14 days after the exposure for signs of clinical toxicity and morbidity.

Group number	Group description	Exposure level (mg/L)	Animals/group	
			Males	Females
1	High	2	5	5

If significant abnormalities remain after 14 days observation the Sponsor will be consulted regarding the requirement to extend the observation period. Following discussion with the Sponsor, if the observation period is extended, the Study Director will prepare a protocol amendment and a cost estimate.

**TEST ATMOSPHERE****Generation of the test atmosphere**

An appropriate method of generation of the test atmosphere will be chosen in order to produce a respirable aerosol with a particle size of between 1 and 4µm, as documented in the EPA OPPTS 870.1300 test guidelines. The test atmosphere will be generated from the bulk test article as supplied by the Sponsor.

**Exposure chamber temperature and relative humidity**

The temperature and relative humidity in the chamber will be monitored continuously and recorded twice hourly. The target temperature and relative humidity ranges will be 20 to 24°C and 30 to 70%, respectively. Values outside these ranges can occur and any deviations will be recorded in the study notes.

**Exposure chamber air flow**

The air flow through the exposure chamber will be monitored continuously and recorded twice hourly. There will not be less than 12 air changes/hour.

**Exposure chamber oxygen concentration**

The oxygen concentration in the exposure chamber will be monitored and recorded twice hourly. The oxygen level will not fall below a minimum value of 19% w/v.

**Nominal concentration**

The test article will be weighed before and after exposures to determine the amount utilized during the exposure period.

**Exposure concentration**

The actual concentration in the exposure chamber will be measured gravimetrically approximately twice hourly during the exposure period.

**Particle size**

The particle size of the atmospheres will be measured prior to exposures, and then hourly for each exposure group using gravimetric methodology. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) will be calculated for each occasion.

**TEST SYSTEM****Species, strain and supplier**

Sufficient rats of the CrI:CD<sup>®</sup>(SD)IGSBR strain will be obtained from a recognised supplier in order to provide enough healthy animals of each sex.

**Specification**

The animals will be obtained as young adults of about 49 days of age on arrival. Each sex ordered in a 15g weight range with minimum body weight for males of 240g and for females 180g. They will be preferably no more than 12 weeks old at start of exposure.

**Environment**

The animals will be housed in a single room, air-conditioned to provide a minimum of 15 air changes/hour. Routinely, the temperature and relative humidity ranges will be 19 to 25°C and 40 to 70%, respectively. Fluorescent lighting will be controlled automatically to give a cycle of 12 hours light (0600 to 1800) and 12 hours dark.

The animals will be housed in groups of five in stainless steel mesh cages of size 55 x 34 x 20 cm, floor area 1870 cm<sup>2</sup>.

**Diet and water**

Throughout the study, the animals will have access *ad libitum* to SQC Rat and Mouse Maintenance Diet No 1, Expanded (Special Diets Services Ltd. Witham). Each batch of diet is analyzed for specific constituents and contaminants. Typical values are presented in Appendix 1.

Main water will be provided *ad libitum* via an automatic watering system or bottles. The water is periodically analyzed for specific contaminants. Typical values are presented in Appendix 2.

While restrained for exposure, animals will not have access to food and water. No contaminants are expected to be present in diet or water at levels which might interfere with achieving the objective of the study.

**ANIMAL HEALTH AND WELFARE**

All procedures to be carried out on live animals as part of this study will be subject to the provisions of United Kingdom National Law, in particular the Animals (Scientific Procedures) Act, 1986.

In order to monitor the welfare of an individual or group of animals, additional observations to those already detailed may be instigated at the discretion of the Study Director. In certain instances this may include treatment as advised by a Covance animal welfare veterinary surgeon.

**PRE-EXPERIMENTAL PROCEDURES****Acclimatisation and health procedures**

All animals will be given a clinical inspection for ill health on arrival. They will be acclimatised for a minimum of 5 days and a veterinary inspection will be performed before the start of exposure to ensure their suitability for study.

**Allocation to treatment group**

Animals will be assigned arbitrarily to the exposure groups during the acclimatisation period. When exposed the weight variation in animals or between groups should not exceed  $\pm 20\%$  of the mean weight.

Treatment group positions in the cage battery will be assigned arbitrarily.

**Identification of the test system**

The animals will be individually identified by tail marking with indelible ink as follows:

**Limit study**

Group number	Group codes	Animals/group	
		Male	Female
1	Pink	1-5	6-10

Cages will be appropriately identified with study information including study number and animal numbers.

**EXPERIMENTAL OBSERVATIONS****Clinical signs**

Animals will be observed for signs of ill health or overt toxicity. Animals will be observed approximately hourly during the exposure period and for the remainder of the exposure day. They will be observed daily during the remainder of the study. Additional observations may be undertaken at the discretion of the Study Director or

the observer. An individual record will be maintained on the clinical condition of each animal.

**Morbidity and mortality**

All animals will be examined at the beginning and the end of the working day to ensure the animals are in good health. Any animal which shows marked signs of ill health may be isolated. Moribund animals will be killed and necropsied.

**Body weights**

Individual body weights will be recorded before and after exposure on Day 1, on Days 2, 8 and 15, and before necropsy.

**TERMINAL PROCEDURES**

**Necropsy and tissue preservation**

All animals including decedents will be subject to necropsy.

An intraperitoneal sodium pentobarbitone overdose will be given prior to exsanguination and a full macroscopic examination will be performed under the general supervision of a pathologist and all lesions will be recorded. The nasal cavity and respiratory tract will be examined and any irritation assessed.

Samples of all gross lesions will be preserved in the appropriate fixative.

**Histology**

No histopathological assessment of tissues will be undertaken in the first instance. However, exposure-related lesions identified macroscopically from animals that survive 24 hours or more will be considered for histopathological examination. The Sponsor will be consulted to see if histopathology is required. If histopathology is required, the Study Director will prepare a cost estimate a protocol amendment. If histopathological assessment of tissues is undertaken this may be in an additional time frame. Microscopic examination of the nasal cavity will not normally be performed as the opening of the nasal cavity for the macroscopic examination disrupts its internal structures.

#### DATA EVALUATION

Any signs of toxicity and mode of death will be assessed. The data will be processed where appropriate to give group mean values and standard deviations.

#### GOOD LABORATORY PRACTICE COMPLIANCE

The study will be performed in compliance with the United Kingdom Statutory Instrument 1999 No. 3106, The Good Laboratory Practice Regulations 1999 and the OECD Principles on Good Laboratory Practice (revised 1997, Issued Jan 1998) ENV/MC/CHEM(98)17

All procedures will be performed in accordance with detailed Standard Operating Procedures. The records to be kept for this study are indicated in the appendices. Wherever appropriate, any change to this protocol will be made by an amendment issued in agreement with the Sponsor.

Protocol review, in-life and report audits will be performed in accordance with Standard Operating Procedures laid down by the Covance Quality Assurance department.

In the event of inspection by an outside authority, the Sponsor will be consulted before the inspectors are permitted access to any of the study records (unless required by law or regulation).

#### REPORTS

The Sponsor will be informed promptly of any significant findings and issued progress reports at appropriate intervals.

Following completion of the study a draft report will be issued. Client comments should be supplied for inclusion into a final document within six months of receipt of the draft document. In accordance with requirements of the UK Medicines Control Agency GLP Monitoring Authority, if no client comments are received within six months of issue, the report will be finalised. Any further changes after this time will be addressed as an amended final report and may result in additional costs.

**ARCHIVE**

All primary data, or authenticated copied thereof, specimens and the final report will be retained in the Covance Laboratories Limited archives for ten years after submission of the final report. At this time the sponsor will be contacted to determine whether the data should be returned, retained or destroyed on their behalf. Sponsors will be notified of the financial implications of each of these options at that time.

Specimens requiring storage deep frozen are specifically excluded from the above. These will be retained for as long as the quality of the material permits evaluation but for no longer than three months after issue of the final report. The Study Sponsor will be notified of the intent to destroy samples and any financial implications before specimens are destroyed on their behalf.

APPENDIX 1  
DIET SUMMARY YEAR ENDING 31 DECEMBER 1999

R&M No 1		Mean	SD
<b>Nutrients</b>			
Moisture	%	10.3	0.8
Crude Fat	%	3.3	0.4
Crude protein	%	15.1	0.5
Crude Fibre	%	4.6	0.4
Ash	%	4.8	0.3
Calcium	%	0.70	0.09
Phosphorus	%	0.52	0.03
Sodium	%	0.24	0.01
Chloride	%	0.38	0.03
Potassium	%	0.76	0.11
Magnesium	%	0.18	0.01
Iron	mg/kg	142	20
Copper	mg/kg	10	1
Manganese	mg/kg	58	6
Zinc	mg/kg	50	8
Vitamin A	iu/g	4.6	1.5
Vitamin E	mg/kg	52	17
<b>Contaminants</b>			
Fluoride	mg/kg	7	2
Nitrate as NaNO <sub>3</sub>	mg/kg	23	10
Nitrite as NaNO <sub>2</sub>	mg/kg	2.2	0.4
Lead	mg/kg	0.27	0.33
Arsenic	mg/kg	ND	ND
Cadmium	mg/kg	0.08	0.03
Mercury	mg/kg	0.00	0.01
Selenium	mg/kg	0.10	0.06
Total Aflatoxins	mcg/kg	ND	ND
Total PCB	mcg/kg	ND	ND
Total DDT	mcg/kg	ND	ND
Dieldrin	mcg/kg	ND	ND
<del>Endosulfan</del>	mcg/kg	ND	ND
Heptachlor	mcg/kg	ND	ND
Malathion	mcg/kg	ND	ND
Total viable organisms	per g	0.35	0.86
Mesophilic spores	per g	3.94	4.51
Salmonellae species	per g	ND	ND
Enteric Bacteriaceae	per g	ND	ND
Escherichia coli	per g	ND	ND
Fungal units	per g	35	36
Antibiotic activity	per g	ND	ND

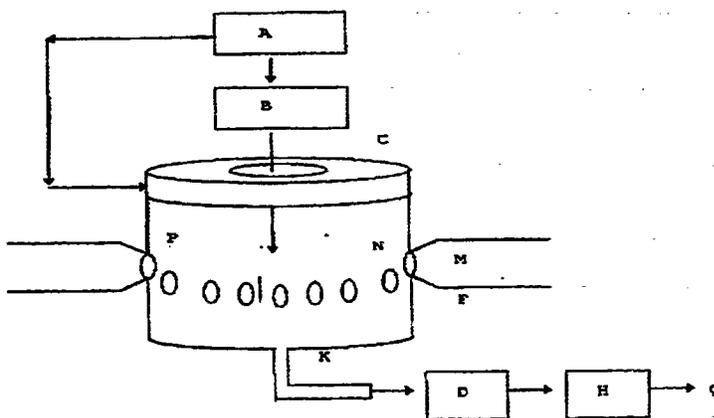
ND = Not detected

APPENDIX 2  
SUMMARY OF WATER ANALYSIS - 1999

Covance water samples sampled at point of use (treated water)			
Parameter	Unit	Range	Mean
Conductivity 20c	uS/cm	1 - 156	141
pH		7.0 - 7.5	7.3
Turbidity	FTU	< 0.15 - 6.00	< 0.42
Nitrate	mg/L NO3	< 1.00 - 6.04	< 3.71
Nitrite	mg/L NO2	< 0.010 - 0.145	< 0.014
Nitrogen ammoniacal	mg/L NH4	< 0.04	< 0.04
Iron	ug/L Fe	< 10 - 366	< 42
Aluminium	ug/L Al	< 10 - 245	< 70
Manganese	ug/L Mn	< 2 - 17	< 4
Colour Type	Hazen	< 2 - 6.3	< 3.3
Aldrin	ug/L	< 0.005	< 0.005
DDT (pp)	ug/L	< 0.010	< 0.010
Dieldrin	ug/L	< 0.005	< 0.005
Endrin	ug/L	< 0.020	< 0.020
HCHL - gamma	ug/L	< 0.005	< 0.005
Copper	ug/L Cu	< 10 - 606	< 89
Lead	ug/L Pb	< 0.5 - 27.0	< 2.1
Zinc	ug/L Zn	< 20 - 321	< 49
Chloride	mg/L Cl	< 5.0 - 17.2	< 14.9
Sulfate	mg/L SO4	< 0.2 - 32.5	< 27.2
Calcium	mg/L Ca	< 2.0 - 14.3	< 12.5
Magnesium	mg/L Mg	< 0.10 - 3.31	< 2.70
Sodium	mg/L Na	< 1.00 - 13.00	< 10.79
Potassium	mg/L K	< 0.20 - 1.63	< 1.39
Phosphorus	ug/L P	< 100 - 1090	< 925
Hardness total	mg/L Ca	< 10 - 19	< 18
Alkalinity total	mg/L HCO3	< 3.0 - 26.9	< 15.4
Total coliforms	No/100ml	0	0
Faecal coliforms	No/100ml	0	0
Escherichia coli	No/100ml	0	0
Chlorine free	mg/L Cl	< 0.05 - 0.05	< 0.05
Chlorine total	mg/L Cl	< 0.05 - 0.18	< 0.07
Colony 1 day 37c	No/ml	0 - 2600	68
Colony 3 day 22c	No/ml	0 - 4080	144

APPENDIX 3

SYSTEM FOR NOSE-ONLY EXPOSURE



- |                               |   |
|-------------------------------|---|
| A - Air supply                | H - Relative humidity hygrometer                |
| B - Aerosol generator         | M - Animal holding tube                         |
| C - Diluent air cyclone inlet | N - Atmosphere sampling port                    |
| D - Atmosphere filter         | P - O <sub>2</sub> and temperature sensors port |
| F - Animal exposure stage     | Q - Flow meter                                  |
| K - Atmosphere outlet         |   |

**APPENDIX 4  
TOXICITY ASSESSMENT CRITERIA**

The data obtained in the single exposure inhalation study can be compared with the toxicity classification below:

Environmental Protection Agency (USA), Prevention, Pesticides and Toxic Substances (7101), EPA 712-C-98-189 August 1998, Health Effects Test Guidelines OPPTS 870.1000, Acute Inhalation Toxicity Testing - Background

Toxicity category by inhalation	LC <sub>50</sub> (mg/L)
I	≤ 0.05
II	> 0.05 - 0.5
III	> 0.5 - 2.0
IV	> 2.0

**APPENDIX 5  
STUDY RECORDS**

The following study records will be routinely maintained and will include but may not be limited to the following:

Definitive protocol  
Protocol amendment(s)  
File notes(s)  
Study schedule  
Study correspondence  
Any despatch/receipt of samples from Covance

Dispensary information pertaining to:  
Test article receipt  
Test article description  
Test article usage  
Test article disposal  
Preparation of dosing formulations (if appropriate)

Animal house information pertaining to:  
Diet batches used  
Diet and water analysis  
Supplier's animal data  
Acceptability and randomisation of animals  
Details of experimental environment

• - central records maintained

Animal house experimental procedures, observations and recording as listed in the protocol

The following data will be maintained if the analyses are required by protocol and performed by Covance:

Inhalation chemistry  
Macro/micro pathological observations and recording as specified in the protocol

Statistical analyses (if appropriate)

**APPENDIX 6  
STUDY REPORTS**

**Draft report**

An unaudited draft report will be issued for the study Sponsor's comments. The report will be prepared to contain the following information:

The name and address of the testing facility/s and the location of all raw data and final report.

The objectives and procedures stated in the approved protocol including any amendments made to the original protocol and any unforeseen circumstances which may have affected the quality or integrity of the study.

The identity of the test and control substances, by name or code number, their quality or purity and accuracy of formulation will be presented if appropriate. The experimental design including study start and completion dates, dose levels, route, frequency and duration of dosing.

The supplier, species, strain and sex of the animals and the method of identification.

The reports of the individual scientists involved in the study.

Data collected and pertaining to the observations as indicated in the protocol will be presented in the report unless considered not appropriate by the Study Director. In these circumstances a textual comment will describe any effects, relationship or absence thereof to dosing.

Other data not specified in the above sections (e.g. data supplied by the Sponsor or suppliers) may be reported where appropriate.

**Final report**

The final report will be produced on paper (2 bound, 1 unbound) following quality assurance evaluation of the complete draft report. In addition to all the details described for the draft report it will contain the Study Directors signature, other

scientists involved in the study as authentication of the report and a statement that the study and the report have been subject to quality assurance evaluation.

**Electronic reports**

An electronic copy of the final report above may be made available on request from the Sponsor. The study report/s will be provided in PDF format unless agreed otherwise by Covance before the start of the study. Reports requiring specialised Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost.

It should be noted that an electronic final report will be despatched only at the request of the Sponsor and will contain, to the best of our knowledge, a full copy of the available information presented in the original and verified hard copy of the final report. However, the electronic copy will not be subject to quality assurance approval. Covance will accept no responsibility for subsequent operations carried out on this electronic information, or copies thereof, after despatched to the Sponsor. Furthermore the electronic copy will be scanned by Covance prior to dispatch for the presence of computer viruses; however, we advise the Sponsor to recheck this prior to accessing as no warranty can be given as to its being virus-free.

**APPENDIX 7  
RESPONSIBLE PERSONNEL**

<b>Study Director</b>	<b>N M Shepherd</b>
<b>Deputy Study Director</b>	<b>A C Gibbs</b>
<b>Head of Pathology</b>	<b>J Glaister</b>
<b>Head of Statistics</b>	<b>C Gardner</b>
<b>Inhalation Chemistry</b>	<b>B Canham</b>
<b>Formulations</b>	<b>B Halliday</b>
<b>Animal house supervisor</b>	<b>J Gladstone</b>
<b>Animal health and welfare</b>	<b>A Bedford</b>
<b>Necropsy</b>	<b>I Wilkins</b>
<b>Histology</b>	<b>S Brogden</b>
<b>Data processing</b>	<b>N Darwent</b>
<b>Head of Quality Assurance</b>	<b>S White</b>

**Proposed Dates**

<b>Animals on site &amp; Experimental start date</b>	<b>April 2000</b>
<b>First treatment</b>	<b>April 2000</b>
<b>Study termination</b>	<b>April / May 2000</b>
<b>Pathology completed &amp; Experimental completion date</b>	<b>April / May 2000</b>
<b>Draft report</b>	<b>June 2000</b>

A change to the Study Director will be documented by protocol amendment, other changes to personnel or dates will be documented in study records.

**Distribution**

Personnel above. Animal House Supervisor (2 copies). Manager AH5.3. Resource management. (scheduling). Resource management (costing). C Springall.

APPENDIX 8  
PROTOCOL APPROVAL

  
\_\_\_\_\_  
H Okada  
Director  
Hodogaya Chemicals (USA), Inc.      23 Mar 2000  
Date

  
\_\_\_\_\_  
N M Shepherd  
Study Director  
Covance Laboratories Ltd      17 March 2000  
Date

  
\_\_\_\_\_  
D Everett BSc CBiol FIBiol  
Head of Toxicology Study Directors  
Covance Laboratories Ltd      17 Mar 00  
Date

  
\_\_\_\_\_  
J Gardner BSc v.Biol MIBiol  
Head, Ethical Compliance  
Deputy Home Office Project Licence Holder  
Project Licence Number:PPL 60/2100 (1)  
Covance Laboratories Ltd      17 March 2000  
Date

## Protocol Amendment

<b>Study Title</b>	TP-415 Toner: Single Exposure (Nose-only) Toxicity Study in the Rat
<b>Data Requirement</b>	Environmental Protection Agency (USA) Prevention, Pesticides and Toxic Substances (7101) EPA 712-C-96-193 August 1998. Health Effects Test Guideline OPPTS 870.1300 Acute Inhalation Toxicity
<b>Study Director</b>	N M Shepherd
<b>Sponsor</b>	HODOGAYA CHEMICAL (USA), INC. 123 Main Street, White Plains N.Y. 10601 USA
<b>Study Monitor</b>	Mr K Kashima Hodogaya Chemical Co., Ltd 68-2 Horikawa-cho Saiwai-ku Kawasaki-ahi, 212-8588 JAPAN
<b>Test Facility</b>	Covance Laboratories Ltd Otley Road, Harrogate North Yorkshire HG3 1PY ENGLAND
<b>Covance Study Number</b>	558/11
<b>Amendment Number</b>	Amendment Number 1
<b>Page Number</b>	1 of 3

**COVANCE**  
THE DEVELOPMENT SERVICES COMPANY

The following amendment documents revisions to the protocol to document the Sponsors request for the storage of a sample of the test article.

**TEST ARTICLE**

The protocol requires the test article to be disposed of in accordance with the Sponsors instructions using standard procedures. At the request of the Sponsor 20g of the remaining TP-415 Toner (Covance dispensary number CHD 0343/00-0558) will be retained by Covance, Harrogate for a period of 2 years. The remaining test article will be discarded.

Covance Study Number: 558/11  
Protocol Amendment Number: 1

AMENDMENT APPROVAL

  
Hiroaki OKADA  
Study Director  
Hodogaya Chemical Co., Ltd

21 Oct 2000  
Date

  
N M Shepherd BSc  
Study Director  
Covance Laboratories Ltd

20 October 2000  
Date

  
Dr P Norris PhD DABT  
Section Manager - Inhalation Toxicology  
Covance Laboratories Ltd

20 October 2000  
Date

### CERTIFICATE OF AUTHENTICITY

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