FOREWORD INTRODUCTION

COPPER MONOCHLORIDE

CAS N°: 7758-89-6

SIDS Initial Assessment Report

For

SIAM 21

Washington D.C., USA, 18-21 October 2005

1. Chemical Name:	**Copper monochloride**
2. CAS Number:	**7758-89-6**
3. Sponsor Country:	Republic of Korea Contact Point: Myungjin Kim National Institute of Environmental Research (NIER). Kyongseo-dong, Seo-gu, Incheon, 404-708, Korea Tel: +82-(0)32-560-7216 FAX: +82-(0)32-560-7256 E-mail: kimmj4@me.go.kr
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	
• Process used	
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	This substance is sponsored by Korea. The assessment process was started in 2004. National Institute of Environmental Research of Korea conducted a literature search, reviewed submitted data and prepared documents for SIAM 21.
7. Review Process Prior to the SIAM:	National Institute of Environmental Research of Korea peer-reviewed the documents and evaluated the quality.
8. Quality check process:	National Institute of Environmental Research of Korea peer-reviewed selected endpoints and verified the data in SIDS dossier with original studies.
9. Date of Submission:	22 July 2005
10. Comments:	The current assessment focuses exclusively on copper monochloride and the results of tests performed with copper monochloride. This assessment should be considered as a contribution to an overall assessment of copper and copper compounds. The conclusions reached in this assessment only apply to copper monochloride, acknowledging that other test

results with other copper compounds could lead to revisions of these conclusions.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	7758-89-6
Chemical Name	Copper monochloride
Structural Formula	$Cu^{+}\ Cl^{-}$

SUMMARY CONCLUSIONS OF THE SIAR

Note: The current assessment focuses exclusively on copper monochloride and the results of tests performed with copper monochloride. This assessment should be considered as a contribution to an overall assessment of copper and copper compounds. The conclusions reached in this assessment only apply to copper monochloride, acknowledging that other test results with other copper compounds could lead to revisions of these conclusions.

Human Health

There are no reliable acute oral toxicity results available. In an acute dermal toxicity study (OECD TG 402), one group of 5 male rats and 5 groups of 5 female rats received doses of 1000, 1500 and 2000 mg/kg bw via dermal application for 24 hours. The LD_{50} values of copper monochloride were 2,000 mg/kg bw or greater for male (no deaths observed) and 1,224 mg/kg bw for female. Four females died at both 1500 and 2000 mg/kg bw, and one at 1,000 mg/kg bw. Symptom of the hardness of skin, an exudation of hardness site, the formation of scar and reddish changes were observed on application sites in all treated animals. Skin inflammation and injury were also noted. In addition, a reddish or black urine was observed in females at 2,000, 1,500 and 1,000 mg/kg bw. Female rats appeared to be more sensitive than male based on mortality and clinical signs.

No reliable skin/eye irritation studies were available. The acute dermal study with copper monochloride suggests that it has a potential to cause skin irritation.

In repeated dose toxicity study performed according to OECD TG 422, copper monochloride was given orally (gavage) to Sprague-Dawley rats for 30 days to males and for 39 – 51 days to females at concentrations of 0, 1.3, 5.0, 20, and 80 mg/kg bw/day. The NOAEL value was 5 and 1.3 mg/kg bw/day for male and female rats, respectively. No deaths were observed in male rats. One treatment-related death was observed in female rats in the high dose group. Erythropoetic toxicity (anemia) was seen in both sexes at the 80 mg/kg bw/day. The frequency of squamous cell hyperplasia of the forestomach was increased in a dose-dependent manner in male and female rats at all treatment groups, and was statistically significant in males at doses of ≥20 mg/kg bw/day and in females at doses of ≥5 mg/kg bw/day doses. The observed effects are considered to be local, non-systemic effect on the forestomach which result from oral (gavage) administration of copper monochloride.

An *in vitro* genotoxicity study with copper monochloride showed negative results in a bacterial reverse mutation test with *Salmonella typhimurium* strains (TA 98, TA 100, TA 1535, and TA 1537) with and without S9 mix at concentrations of up to 1,000 µg/plate. An i*n vitro* test for chromosome aberration in Chinese hamster lung (CHL) cells showed that copper monochloride induced structural and numerical aberrations at the concentration of 50, 70 and 100 µg/mL without S9 mix. In the presence of the metabolic activation system, significant increases of structural aberrations were observed at 50 and 70 µg/mL and significant increases of numerical aberrations were observed at 70 µg/mL. In an i*n vivo* mammalian erythrocyte micronucleus assay, all animals dosed (15 - 60 mg/kg bw) with copper monochloride exhibited similar PCE/(PCE+NCE) ratios and MNPCE frequencies compared to those of the negative control animals. Therefore copper monochloride is not an *in vivo* mutagen.

Concerning the carcinogenicity, there was insufficient information to evaluate the carcinogenic activity of copper monochloride.

In the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), copper monochloride was given orally (gavage) to Sprague-Dawley rats for 30 days to males and for 39 – 51 days to females at concentrations of 0, 1.3, 5.0, 20, and 80 mg/kg bw/day. The NOAEL of copper

monochloride for fertility toxicity was 80 mg/kg bw/day for the parental animals. No treatment-related effects were observed on the reproductive organs and the fertility parameters assessed. For developmental toxicity the NOAEL was 20 mg/kg bw/day. Three of 120 pups appeared to have icterus at birth; 4 of 120 pups appeared runted at the highest dose tested (80 mg/kg bw/day).

Environment

Copper monochloride exists as a white crystalline powder or as cubic crystals. It is slightly soluble in water (47 mg/L at 20 °C). It has a density of 4.14 g/cm^3 at 25 °C, a melting point of 430 °C and a boiling point of 1,400 °C. A vapour pressure is not assignable due to the high melting point. When considering inorganic copper species the partition coefficient in n-octanol/water is not applicable.

In the atmosphere, copper monochloride turns green and the substance turns blue to brown on exposure to light in the presence of moisture. The copper (I) ion is unstable in aqueous solution, tending to disproportionate to copper (II) and copper metal unless a stabilizing ligand is present. The copper (I) compounds stable in water are insoluble ones such as the sulfide, cyanide and fluoride. The fugacity based environment fate model is of limited use to inorganic substances.

The results from studies with aquatic organisms are as follows:
Fish (*Oryzias latipes*): LC_{50} (96 h) = 0.039 mg/L
Invertebrates (*Daphnia magna*): EC_{50} (48 h) = 0.25 mg/L
Green algae (*Pseudokirchneriella subcapitata*): E_rC_{50} (72 h) = 0.058 mg/L
These toxicity values are based on total dissolved concentrations (copper chloride) which do not normalize for bioavailability influenced parameters. In natural environment, toxicity threshold of copper monochloride can be modified with variation of pH, water hardness and dissolved organic matter.

Exposure

In Korea the estimated production volume of copper monochloride was 8000, 6000, and 4000 tonnes/year in 2002, 2003, and 2004. In Denmark the estimated production volume of copper monochloride was 2.7 tonnes/year in 2003. Copper monochloride is produced by reaction of copper with chloride gas at 700 °C in a closed system. Copper monochloride occurs in nature as the mineral nantokite.

Copper monochloride has a wide variety of uses such as in the denitration of cellulose, in gas analysis to absorb carbon monoxide, as a catalyst for organic reactions, as a decolorizer and a desulfuring agent in petroleum industry, as a condensing agent for soaps, fats and oils, as a catalyst for manufacturing CO and H_2, and as a raw material for manufacturing coloring agents.

Korea has periodically collected the monitoring data of the treated sewage and the exhaust gas for copper concentration in the manufacturing process. The measured concentrations of copper in the treated sewage and the exhaust gas were not detected and 4 mg/m^3 respectively, which were below the effluent and emission standard of 3 mg/L and 10 mg/m^3 in Korea.

In the production and processing facilities of Korea, workers might be exposed to copper monochloride dust by inhalation during putting or packaging the raw material. Occupational exposure is controlled with personal protective equipments such as dust masks, gloves and protective clothing and with ventilation. The 8hr-TWA concentrations of dust at the workplace in copper monochloride and dye manufacturing factories ranged from 0.5 to 0.9 mg/m^3, in case of copper ranging from N.D. to 0.0007 mg/m^3.
Copper monochloride is used as a raw material for coloring agents such as copper phthalocyanine blue crude, the C.I. No. Acid Blue 62, 40 and the C.I. Reactive Blue 19 and a catalyst for manufacturing CO and H_2 in Korea and consumer exposure is not expected in the Sponsor country.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: This chemical is currently a low priority for further work. The chemical possesses properties indicating hazards for human health (acute toxicity, repeated dose toxicity, uncertainty regarding developmental toxicity). Based on the data presented by the Sponsor country (relating to production in one country which accounts for an unknown fraction of the global production and relating to the use pattern in one country), the

exposure is low at the workplace. There is no consumer exposure to copper monochloride in the Sponsor country. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: This chemical is a candidate for further work. The chemical possesses properties indicating hazards for environment (acute aquatic toxicity). Based on the use pattern of this chemical, member countries are invited to perform an exposure assessment and if necessary a risk assessment for this compound.

Consideration should be given to the assessment of other copper compounds in the OECD HPV Chemicals Programme.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number:	7758-89-6
IUPAC Name:	Copper monochloride
EINECS No:	231-842-9
Molecular Formula:	CuCl
Structural Formula:	$Cu^+ Cl^-$
Molecular Weight:	99.00 (Merck)
Synonyms:	Copper chloride (CuCl)
	Copper chloride (Cu_2Cl_2)
	Copper(1+) chloride
	Copper(I) chloride
	Cuprous chloride (Cu_2Cl_2)
	Cuprous chloride (CuCl) (5)
	Dicopper dichloride
	Chloride medny (CZECH)
	Cuprous chloride
	Cuprous dichloride (3)

1.2 Purity/Impurities/Additives

Purity:	98.7 %
Impurities:	0.0055 % Iron (Fe)
	0.0035 % Nickel (Ni)
	0.0030 % Zinc (Zn)
	0.0010 % Lead (Pb)
	0.35 % Copper dichloride ($CuCl_2$) (11)

Additives:

1.3 Physico-Chemical Properties

Copper monochloride is a white crystalline powder or cubic crystals (1).

Table 1 Summary of physico-chemical properties for copper monochloride

Property	Value	Reference
Physical state	Solid	
Melting point	430 °C	(1), (3), (4)
Boiling point	1,400 °C	(1)
Density	4.14 g/cm^3 at 25 °C	(1)
Vapour pressure	Not applicable; inorganic salt	
Water solubility	47 mg/L at 20 °C	(4)
Partition coefficient n-octanol / water (log value)	Not applicable; inorganic salt	
Dissociation constant (Log ß)	3.0±0.1 at 25°C	(2)

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes, Manufacturing Processes and Use Patterns

In Korea the estimated production volume of copper monochloride was approx. 8 000, 6 000, and 4 000 tonnes/year in 2002, 2003, and 2004, respectively. Estimated usage of the substance was appox. 1 350, 40, and 400 tonnes/year in 2002, 2003, and 2004, respectively (11). In Denmark the estimated production volume of copper monochloride was 2.7 tonnes/year in 2003 (15).

In Korea copper monochloride is produced by reaction of Cl_2 gas and copper under 700 °C in a closed system.

$2Cu + Cl_2 (g) \rightarrow 2CuCl$

The two raw materials are transferred to a reactor through a hoist and the reacted material is cooled. After auto-pulverizing, the products are packed, and sealed up (11).

The general uses of copper monochloride are as follows;

It is used in the denitration of cellulose, in gas analysis to absorb carbon monoxide, as a catalyst for organic reactions, a decolorizer and a desulfuring agent in petroleum industry, and a condensing agent for soaps, fats and oils (1).

In Korea, copper monochloride is used as a raw material for coloring agents such as copper phthalocyanine blue crude, the C.I. No. Acid Blue 62, the C.I. No. Acid Blue 40 and the C.I. Reactive Blue 19 and a catalyst for manufacturing CO and H_2 (11).

2.2 Environmental Exposure and Fate

2.2.1 Environmental Exposure

Copper monochloride occurs in nature as the mineral nantokite (1).

In Korea, one company produces copper monochloride. Copper monochloride is produced in a closed system and may be emitted to the atmosphere and water. In the manufacturing process, wastewater containing copper ions is reused in the production of copper dichloride. And then the sewage is treated in the facilities and is discharged to wastewater treatment plant. The measured

concentration of copper in the treated sewage was approximately 2 mg/L. This wastewater is transferred into the municipal sewage treatment plant. It is emitted into the river and copper concentration in the discharged wastewater is not detected. In the stack of the factory, filtered dust is emitted to the atmosphere. The measured concentration of copper in the exhaust gas was approximately 4 mg/m^3 (11).

2.2.2 Environmental Fate

In the atmosphere, copper monochloride turns green and the substance turns blue to brown on exposure to light in the presence of moisture (1).

The copper (I) ion is unstable in aqueous solution, tending to disproportionate to copper (II) and copper metal unless a stabilizing ligand is present. The copper (I) compounds stable in water are insoluble ones such as the sulfide, cyanide and fluoride (16).

The fugacity based environment fate model is of limited use to inorganic substances. No data were available for bioaccumulation of copper monochloride.

2.3 Human Exposure

2.3.1 Occupational Exposure

In the production facility in Korea, workers are potentially exposed to dust of copper monochloride in the packing area where local ventilation systems are equipped concurrently with general ventilation systems. The 8hr-TWA concentration of total dust ranged from 0.6 to 0.9 mg/m^3, which is below the occupational exposure limit of 10 mg/m^3 (11).

When workers put the raw materials including copper monochloride into a reactor in the dye manufacturing, the negative pressure of the reactor reduced dust exposure. According to the monitoring data, the total dust concentration levels in the workplace were approximately 0.5 mg/m^3, in case of copper ranging from N.D. to 0.0007 mg/m^3. These values were less than the occupational exposure limit of 10 mg/m^3 as total dust and 1 mg Cu/m^3, respectively (11).

There are no monitoring data available in a CO or a H_2 manufacturing plant where a small amount of copper monochloride was used as a catalyst (11).

The following controls are being applied in all facilities in Korea: engineering controls; administration controls such as a regulation of industrial safety and health and safe work practices within a company; and the use of personal protective equipment (PPE) such as dust masks, gloves, and protective clothing (11).

2.3.2 Consumer Exposure

Copper monochloride is used as a raw material for coloring agents such as copper phthalocyanine blue crude, the C.I. No. Acid Blue 62, the C.I. No. Acid Blue 40, and the C.I. Reactive Blue 19 and a catalyst for manufacturing CO and H_2 in Korea. Consumer exposure is not expected in the sponsor country (11).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No results are available with copper monochloride

3.1.2 Acute Toxicity

Acute Oral Toxicity

There is no acute oral toxicity data available for copper monochloride.

Acute Dermal Toxicity

An acute dermal toxicity study was performed using Sprague-Dawley rats in accordance with OECD TG 402 and GLP (11). One group of five male and five groups each of five females were moistened with copper monochloride for 24 hours at doses of 2,000 mg/kg bw and 0, 500, 1,000, 1,500 or 2,000 mg/kg bw, respectively. During the study, there was no death in male rats. Four females died at both 1,500 and 2,000 mg/kg bw, and one at 1,000 mg/kg bw.

On application sites, hardness of skin, exudation, formation of scar/falling off scar, and reddish changes were observed in all treated animals. Reddish or black urine was observed in female rats at 1,000 mg/kg bw or above. All survived rats were considered to gain normal body weights throughout the study except for 1,500 mg/kg bw treated female rats. The body weight of this group was significantly reduced on day 8 post initial application because of one moribund rat. No abnormalities were observed in all survived animals.

Conclusion

There is no available acute oral and inhalation toxicity for copper monochloride. The acute lethal doses (LD50 values) of copper monochloride by single dermal administration were considered to be greater than 2,000 mg/kg bw and 1,224 mg/kg bw for male and female rats, respectively.

3.1.3 Skin/Eye Irritation

No reliable skin/eye irritation studies were available. The observations from an acute dermal study with copper monochloride suggest that it has a potential to cause skin irritation.

3.1.4 Skin Sensitization

There is no information available on skin sensitization.

3.1.5 Repeated dose toxicity

A repeated dose toxicity study was conducted according to OECD TG 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Screening Test (7). In this study, Sprague-Dawley rats were orally administered with copper monochloride at 0, 1.3, 5.0, 20, and 80 mg/kg bw/day for 30 days for males and for 39 - 51 days for females. Each group consisted of twelve rats.

No death was observed in male rats. Three deaths were observed in the 80 mg/kg bw/day treated female group. One death on day 1 of administration was treatment-related and the others were due to errors of dosage. There were statistical decreases in red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH), and increases in white blood cell count (WBC) and platelet (PLT) in the 80 mg/kg bw/day male groups. In the same group, neutrophil (NEU) was increased compared with the controls. These findings were consistent with the hematological results observed in microcytic hypochromic anemia, also considered to be the primary cause of bone marrow hyperplasia of femur. For females, a statistically significant decrease on in MCH and an increase in PLT were observed in the 80 mg/kg bw/day group. These findings were similar to those of males, but other values were different from those of males due to a sexual difference.

Bone marrow hyperplasia of femur was found in 8 males of the 80 mg/kg bw/day group. The frequency of squamous cell hyperplasia of stomach was significantly higher than the controls in the 20 and 80 mg/kg bw/day male groups, which were attributed to copper monochloride. The same findings in the stomach was observed in female rats receiving 5 mg/kg bw/day and the symptom was more severe than that of male rats.

Conclusion

Repeated oral dosing of copper monochloride resulted in one death and an anemic status of females, and microcytic hypochromic anemia and bone marrow hyperplasia of femur of males in the 80 mg/kg bw/day group. In addition, the frequency of squamous cell hyperplasia of the forestomach mucous membrane was increased in a dose-dependent manner in male and female rats at all treatment groups, but these findings were statistical significant in males at doses of ≥20 and in females at doses of ≥5 mg/kg bw/day. The observed effects are considered to be local, non-systemic effecst on the forestomach which result from oral (gavage) administration of copper monochloride. From these results, the NOAEL was 5 mg/kg bw/day for male rats and 1.3 mg/kg bw/day for female rats.

3.1.6 Genetic toxicity

3.1.6.1 *In vitro* Studies

Bacterial tests

A bacterial reverse mutation test was performed in accordance with OECD TG 471 and GLP (6). Copper monochloride was negative in the bacterial reverse mutation assay using *Salmonella typhimurium* (strains TA 98, TA 100, TA 1535 and TA 1537) and *Escherichia coil* (strain WP2 *uvr*A) with and without a metabolic activation system at 3.7, 11.1, 33.3, 100, 300, and 1,000 μg/plate. All mean values of revertant colony counts on negative control treatments fell within acceptable ranges, while positive control treatments induced clear increases in the mean values of revertant colony counts.

Table 2 Results of bacterial reverse mutation assay with copper monochloride

Tester strain	Chemical treated	Dose (µg/plate)	Colonies/plate (mean ± SD)	
			Without S9 mix	With S9 mix
TA 98	Test item	0	34 ± 11	23 ± 3
		3.7	26 ± 4	26 ± 7
		11.1	36 ± 7	24 ± 2
		33.3	34 ± 6	26 ± 3
		100	32 ± 7	27 ± 3
		300	27 ± 6	-[2]
		1,000	-[1]	-[2]
TA 100	Test item	0	114 ± 6	109 ± 19
		3.7	114 ± 13	122 ± 13
		11.1	128 ± 9	114 ± 15
		33.3	134 ± 17	109 ± 7
		100	132 ± 13	125 ± 15
		300	116 ± 6	-[1]
		1,000	-[1]	-[1]
TA 1535	Test item	0	14 ± 4	12 ± 2
		3.7	17 ± 2	13 ± 1
		11.1	10 ± 0	11 ± 7
		33.3	13 ± 4	13 ± 5
		100	12 ± 3	14 ± 7
		300	17 ± 3	13 ± 3
		1,000	10 ± 4	15 ± 10
TA 1537	Test item	0	10 ± 1	11 ± 5
		3.7	7 ± 2	12 ± 5
		11.1	8 ± 2	7 ± 3
		33.3	9 ± 3	7 ± 3
		100	6 ± 3	9 ± 1
		300	9 ± 2	-[1]
		1,000	-[2]	-[1]
WP2 *uvr*A	Test item	0	13 ± 6	15 ± 3
		3.7	13 ± 3	10 ± 1
		11.1	12 ± 4	11 ± 3
		33.3	10 ± 1	10 ± 4
		100	10 ± 6	6 ± 1
		300	9 ± 3	-[1]
		1,000	6 ± 0	-[1]
Positive control				
TA 98	2-NF	1.0	356 ± 23 [SS]	
	2-AA	2.0		853 ± 34 [SS]
TA 100	SA	0.5	405 ± 40 [SS]	
	2-AA	2.0		803 ± 48 [SS]
TA 1535	SA	0.5	286 ± 23 [SS]	
	2-AA	5.0		236 ± 8 [SS]
TA 1537	9-AA	50	211 ± 25 [SS]	
	2-AA	5.0		373 ± 38 [SS]
WP2 *uvr*A	4-NQ	2.0	576 ± 66 [SS]	
	2-AA	10		522 ± 15 [SS]

[1]; No colony count and thin lawn but doubt as to whether the microscopic colonies are mutants or enlarged background colonies

[2]; Complete killing

[SS]: Statistical significance was observed ($p \leq 0.01$).

2-NF:2-Nitrofluorene, 2-AA:2-Aminoanthrancene, SA:Sodiumazide, 9-AA:9-Aminoacridine, 4-NQ:4-Nitroquinoline

Conclusion

Copper monochloride did not exhibit mutagenic activity to any test strains under the conditions employed for this test.

Non-bacterial test

The clastogenic potential of copper monochloride was tested in an in vitro chromosome aberration study using Chinese Hamster Lung (CHL) cells, both in the absence and the presence of metabolic activation system (S9 mix) (9). This test was performed in accordance with OECD TG 473 and GLP.

Cells were treated for 6 hrs followed by 18 hrs of recovery period both in the absence and in the presence of metabolic activation system. The selected dose levels in the absence of metabolic activation system were 50, 70 and 100 μg/mL and in the presence of metabolic system were 20, 50 and 70 μg/mL, respectively.

The treatment of copper monochloride induced an increase in the proportion of cells with structural and numerical aberrations in the absence of the metabolic system. In the presence of the metabolic system, significant increases in the proportion of cells with structural aberrations and numerical aberrations were observed at 50 and 70 μg/mL and 70 μg/mL dose level, respectively.

Table 3 Summary of structural and numerical chromosome aberrations –S9 and +S9 mix, 6 hour treatment 18 hour recovery (6+18), confirmation experiment

Treatment (μg/ml)		Replicate	Cells counted	Cells with structural aberrations (-gap)	Cells with numerical aberrations	Mitotic index (mean)
-S9 6+18	Distilled water	A	100	0	0	7.5
		B	100	0	1	7.2
		Total	200	0	1	7.4
	50	A	100	5	3	7.2
		B	100	7	4	6.9
		Total	200	12 [ss]	7 [ss]	7.1
	70	A	100	12	10	2.5
		B	100	10	8	3.1
		Total	200	22 [ss]	18 [ss]	2.8
	100	A	100	16	11	4.4
		B	100	20	9	2.5
		Total	200	36 [ss]	20 [ss]	3.5
	MMC 0.1μg/ml	A	100	17	0	7.5
		B	100	19	0	7.7
		Total	200	36 [ss]	0 [NS]	7.6
+S9 6+18	Distilled water	A	100	1	0	9.1
		B	100	1	1	9.0
		Total	200	2	1	9.1
	20	A	100	4	3	8.9
		B	100	2	0	9.2
		Total	200	6 [NS]	3 [NS]	9.1
	50	A	100	5	1	9.5
		B	100	9	2	8.9
		Total	200	14 [ss]	3 [NS]	9.2
	70	A	100	12	3	7.4
		B	100	23	7	4.5
		Total	200	35 [ss]	10 [ss]	6.0
	B(a)P 5μg/ml	A	100	33	1	7.1
		B	100	31	1	6.8
		Total	200	64 [ss]	2 [NS]	7.0

[SS]: Statistical significance was observed ($p \leq 0.05$).

[NS]: No statistical significance was observed.

Conclusion

Copper monochloride exhibited clastogenic activity in cultured CHL cells under the conditions employed for this test.

3.1.6.2 *In vivo* Studies

A mammalian erythrocyte micronucleus test was performed in accordance with OECD TG 474 (10). Each group was composed of six mice. Copper monochloride was orally administered, and negative control (0.5 % CMC) and positive control (2 mg/kg mitomycin C) were administered by intraperitoneal (I.P.), respectively. The copper monochloride treated group exhibited similar PCE/(PCE + NCE) ratios and MNPCE frequencies compared to those of the negative control group.

Table 4 Summary of PCE/(PCE + NCE) ratio and MNPCE frequency

Treatment group	Dose (mg/kg bw)	PCE/(PCE+NCE) (mean ±S.D.)	MNPCE per 1,000 PCE (mean ± S.D.)
Vehicle	0	0.500 ± 0.004	0.9 ± 0.5
Copper monochloride	15	0.500 ± 0.005	0.8 ± 0.4
	30	0.497 ± 0.011	0.9 ± 0.6
	60	0.500 ± 0.008	0.8 ± 0.4
Mitomycin C	2	0.495 ± 0.003	84.5* ± 5.2

*: Indicate significant difference at $p \leq 0.01$ level

MNPCE: Micronucleated polychromatic erythrocyte, PCE: Polychromatic erythrocyte,

NCE: Normochromatic erythrocyte

Conclusion

Copper monochloride did not induce micronuclei in the mice bone marrow cells for this test.

3.1.7 Carcinogenicity

No results are available with copper monochloride

3.1.8 Reproductive Toxicity

Effects on Fertility

A fertility toxicity study with copper monochloride was performed in accordance with OECD TG 422 (7). Sprague-Dawley rats were treated orally at doses of 0, 1.3, 5.0, 20 and 80 mg/kg bw/day. Male and female animals were dosed for 30 days and 39 - 51 days, respectively.

No treatment-related effects were observed on the reproductive organs and the fertility parameters assessed.

Conclusion

The NOAEL of 80 mg/kg bw/day represents the highest test dose in this assay performed in accordance with OECD TG 422.

Developmental toxicity

The study according to the OECD TG 422 provided evaluations of developmental toxicity (6). The offspring delivered by chemical-treated rats had been observed until day 4 of postpartum. Three of 120 pups showed a gross lesion, namely icterus at day 0 in the 80 mg/kg bw/day group with

significant increases, but the effects disappeared by day 4. The incidence of runts (4 of 120 pups) in the 80 mg/kg bw/day was significantly different from the control and was higher than the historical control data. The occurrence of icterus and runts was observed from the same dams (dam 110 and 120) except for one pup with icterus from treated dam 117.

Conclusion

The NOAEL for developmental toxicity was 20 mg/kg bw/day under the conditions employed for this test.

3.2 Initial Assessment for Human Health

No reliable data on acute toxicity via oral or inhalation route was available. The acute dermal LD_{50} of copper monochloride was greater than 2,000 and 1,224 mg/kg bw for male and female, respectively. The evidence of systemic toxicity observed in female rats from the acute dermal study suggests that copper monochloride has a potential to cause skin irritation.

For repeated dose toxicity the NOAEL was 5 mg/kg bw/day for male rats and 1.3 mg/kg bw/day for female rats under the conditions employed for this test. Repeated oral dosing of copper monochloride resulted in one treatment-related death and an anemic status of females, and microcytic hypochromic anemia and bone marrow hyperplasia of femur of males in the 80 mg/kg bw/day group. In addition, the frequency of squamous cell hyperplasia of stomach mucous membrane was increased in a dose-dependent manner in male and female rats at all treatment groups, but these findings were statistically significant in males at doses ≥20 and in females at doses ≥5 mg/kg bw/day.

Copper monochloride was not mutagenic in a bacterial assay using *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA 1537) and *Escherichia coli* (strain WP2 *uvrA*) with and without a metabolic activation system at concentrations of up to 1,000 µg/plate. An i*n vitro* test for chromosome aberration in Chinese hamster lung (CHL) cells showed that copper monochloride induced structural and numerical aberrations at the concentration of 50, 70 and 100 µg/mL without S9 mix. In the presence of the metabolic system, significant increases with the structural and numerical aberrations were observed at 50, 70 and 100 µg/mL concentration levels. In an *in vivo* mammalian erythrocyte micronucleus test, a significant increase in micronuclei in the mice bone marrow was not observed. As a result, copper monochloride is not an *in vivo* mutagen.

The NOAEL for toxicity to fertility of copper monochloride was 80 mg/kg bw/day of the parental animals under experimental conditions. No treatment-related effects were observed on the reproductive organs and the fertility parameters. For developmental toxicity the NOAEL was 20 mg/kg bw/day. Three of 120 pups appeared to have icterus at birth; 4 of 120 pups appeared runted at the highest dose tested (80 mg/kg bw/day).

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute aquatic toxicity tests of copper monochloride were conducted under GLP for fish, daphnia and algae. Copper monochloride was analysed with Inductively Coupled Plasma Atomic Emission Spectrometer (ICP-AES). The stability test was conducted with 1.03 mg/L of copper monochloride in OECD M4 medium. The test substance remained at 74.1 to 74.0 % of its initial concentration during 48 hr. From these data, copper monochloride is considered to be stable in the aquatic test system.

A static test using *Oryzias latipes* was performed in accordance with OECD TG 203. The LC_{50} value of copper monochloride for fish was 0.039 mg/L during 96 hrs and the 95 % confidence limits were 0.032 to 0.048 mg/L.

The mean measured concentrations were 32.0, 29.3, and 20.8 % at 96 hrs. At the end of the test, the ion strength of test solution was higher than the ion strength of the test solution at the end of the test, which was due to the presence of other ions resulted from accumulation of bio-contaminants such as feces of the test organism (14).

Daphnia magna was tested according to the OECD TG 202 under static conditions. Mean measured concentrations ranged from 34.5 to 68.2 % of the nominal concentrations during 48 hrs. The EC_{50} value of copper monochloride for daphnia was 0.25 mg/L during 48 hrs (13).

The 72 hrs alga growth inhibition test with *Pseudokirchneriella subcapitata* was performed based on nominal concentrations. Test concentrations were 0.0094, 0.019, 0.038, 0.075 and 0.15 mg/L but the concentration of copper in the 0.0094 and 0.019 mg/L of test solution were not detected because the limit of detection of the instrument (ICP-AES) is 0.01 mg/L. The measured concentrations remained at 41.6 - 91.8 % of the nominal concentrations above detection limit. The 72 hrs EC_{r50} value was 0.058 mg/L and the EC_{b50} value was 0.057 mg/L (8).

These toxicity values are based on total dissolved concentrations (copper chloride) which do not normalize for bioavailability influenced parameters. In the natural environment, the toxicity threshold of copper monochloride can be modified with variation of pH, water hardness and dissolved organic matter.

4.2 Terrestrial Effects

No results are available for copper monochloride.

4.3 Initial Assessment for the Environment

Copper monochloride exists as a white crystalline powder or as cubic crystals. It is slightly soluble in water (47 mg/L at 20 °C). It has a density of 4.14 g/cm^3 at 25 °C, a melting point of 430 °C and a boiling point of 1,400 °C. A vapour pressure is not assignable due to the high melting point. When considering inorganic copper species the partition coefficient in n-octanol/water is not applicable.

In the atmosphere, copper monochloride turns green and the substance turns blue to brown on exposure to light in the presence of moisture. The copper (I) ion is unstable in aqueous solution, tending to disproportionate to copper (II) and copper metal unless a stabilizing ligand is present. The copper (I) compounds stable in water are insoluble ones such as the sulfide, cyanide and fluoride. The fugacity based environment fate model is of limited use to inorganic substances.

The results from studies with aquatic organisms are as follows:

Fish (*Oryzias latipes*): LC_{50} (96 h) = 0.039 mg/L

Invertebrates (*Daphnia magna*): EC_{50} (48 h) = 0.25 mg/L

Green algae (*Pseudokirchneriella subcapitata*): E_rC_{50} (72 h) = 0.058 mg/L

These toxicity values are based on total dissolved concentrations (copper chloride) which do not normalize for bioavailability influenced parameters. In natural environment, toxicity threshold of copper monochloride can be modified with variation of pH, water hardness and dissolved organic matter.

5 RECOMMENDATIONS

Human health:

This chemical is currently a low priority for further work. The chemical possesses properties indicating hazards for human health (acute toxicity, repeated dose toxicity, uncertainty regarding developmental toxicity). Based on the data presented by the Sponsor country (relating to production in one country which accounts for an unknown fraction of the global production and relating to the use pattern in one country), the exposure is low at the workplace. There is no consumer exposure to copper monochloride in the Sponsor country. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment:

This chemical is a candidate for further work. The chemical possesses properties indicating hazards for environment (acute aquatic toxicity). Based on the use pattern of this chemical, member countries are invited to perform an exposure assessment and, if necessary, a risk assessment for this compound.

Consideration should be given to the assessment of other copper compounds in the OECD HPV Chemicals Programme.

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SIDS DOSSIER

Copper monochloride

CAS No. : 7758-89-6

Sponsor Country: Republic of Korea

Date of submission to OECD: 22 July 2005

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Note: The current assessment focuses exclusively on copper monochloride and the results of tests performed with copper monochloride. This assessment should be considered as a contribution to an overall assessment of copper and copper compounds. The conclusions reached in this assessment only apply to copper monochloride, acknowledging that other test results with other copper compounds could lead to revisions of these conclusions.

1.01 SUBSTANCE INFORMATION

CAS Number	:	7758-89-6
Name (OECD name)	:	Copper monochloride
EINECS-Number	:	231-842-9
Molecular Formula	:	CuCl
Structural Formula	:	

$Cu^+ Cl^-$

Molecular Weight	:	99.00
22.07.2005	:	(2)

1.02 OECD INFORMATION

Sponsor Country	:	Republic of Korea
Lead Organisation	:	National Institute of Environmental Research
Contact person	:	Myungjin Kim
Address	:	Environmental Research Complex
Street	:	Kyongseo-dong, Seo-gu
Postal code	:	404-708
Town	:	Incheon
Country	:	Republic of Korea
Tel	:	+82-(0)32-560 7216
Fax	:	+82-(0)32-560 7256
E-mail	:	kimmj4@me.go.kr

Name of responder (Information on a responder should be provided when companies respond to Lead Organisation or SIDS Contact Points.)

Name	:	Same as above
Address	:	Same as above

1.1 GENERAL SUBSTANCE INFORMATION

Type of Substance	:	Inorganic
Physical State (at 20 °C and 1.013 hPa)	:	Solid
Purity	:	98.7 %
Colour	:	White
Odour	:	Odorless
Reliability	:	(2) Reliable with restrictions 2g - Data from handbook or collection of data
22.07.2005		(16)

1.2 SYNONYMS AND TRADENAMES

Synonym	:	Copper chloride (CuCl) Copper chloride (Cu_2Cl_2) Copper(1+) chloride Copper(I) chloride Cuprous chloride (Cu_2Cl_2)

Cuprous chloride (CuCl)
Dicopper dichloride

Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (10)

Synonym : Chloride medny (CZECH)
Cuprous chloride
Cuprous dichloride

Reliability : (2) Reliable with restrictions
4b - Data from handbook or collection of data
22.07.2005 (7)

1.3 IMPURITIES

CAS No. : 7439-89-6
EINECS No. : 231-096-4
Name : Iron (Fe)
Value : 0.0055 %
Source : Commercial product
22.07.2005 (16)

CAS No. : 7439-92-1
EINECS No. : 231-100-4
Name : Lead (Pb)
Value : 0.0010 %
Source : Commercial product
22.07.2005 (16)

CAS No. : 7440-66-6
EINECS No. : 231-175-3
Name : Zinc (Zn)
Value : 0.0030 %
Source : Commercial product
22.07.2005 (16)

CAS No. : 7440-02-0
EINECS No. : 231-111-4
Name : Nickel (Ni)
Value : 0.0035 %
Source : Commercial product
22.07.2005 (16)

CAS No. : 7447-39-4
EINECS No. : 231-210-2
Name : Copper chloride ($CuCl_2$)
Value : 0.35 %
Source : Commercial product
22.07.2005 (16)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Estimated production : In Korea estimated production volume of copper monochloride was appox. 8,000, 6,000, and 4,000 tonnes/year in 2002, 2003, and 2004, respectively and estimated usage of the substance was appox. 1,346, 37, and 406 tonnes/year in 2002, 2003, and 2004, respectively.
In Denmark estimated production volume of copper monochloride was 2.7

tonnes/year in 2003.
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (16), (21)

1.6.1 LABELLING

Labelling : As in Directive 67/548/EEC
Symbols : (Xn)
(N)
Specific limits : No data
R-phrases : (22) Harmful if swallowed
(50/53) Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
S-phrases : (2) Keep out of the reach of children.
(22) Do not breathe dust.
(60) This material and its container must be disposed of as hazardous waste.
(61) Avoid release to the environment. Refer to special instructions/safety data sheets.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (5)

1.6.2 CLASSIFICATION

Classification : As in Directive 67/548/EEC
Class of danger : Corrosive
R-phrases : (22) Harmful if swallowed
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (5)

Classification : As in Directive 67/548/EEC
Class of danger : Dangerous for the environment
R-phrases : (50) Very toxic to aquatic organisms
(53) May cause long-term adverse effects in the aquatic environment.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (5)

1.6.3 PACKAGING

1.7 USE PATTERN

Type : Industrial
Category : As a catalyst for organic reactions
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (2)

Type : Industrial
Category : As a decolorizer and desulfuring agent in petroleum industry
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (2)

Type : Industrial

Category : In a denitration of cellulose
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (2)

Type : Industrial
Category : As a condensing agent for soaps, fats and oils
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (2)

Type : Industrial
Category : In a gas analysis to absorb carbon monoxide
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (2)

Type : Industrial
Category : In manufacturing copper phthalocyanine blue crude used as a blue pigment
Remark : In Korea copper monochloride is one of the three ingredients for manufacturing copper phthalocyanine blue crude.
Copper phthalocyanine blue crude as a blue pigment is produced by reaction of phthalic anhydride, urea, and copper monochloride as raw materials up to 185 °C
Overall reaction formula is as follows;
$4C_8H_4O_3+4(NH_2)_2CO+CuCl \rightarrow$Copper phthalocyanine blue crude$+H_2O+4CO_2$
Overall use process is gone though reaction of three raw materials, refining, filtering, and packing in ~~a~~ closed system.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (16)

Type : Industrial
Category : As a catalyst
Remark : In Korea copper monochloride is used as a catalyst for manufacturing CO and H_2.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (16)

Type : Industrial
Category : In manufacturing coloring agent
Remark : In Korea copper monochloride is used as an ingredient for manufacturing coloring agents such as the C.I. No. Acid Blue 62, the C.I. No. Acid Blue 40, and the C.I. Reactive Blue 19.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (16)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Source : Production and processing

Remarks : In Korea copper monochloride is produced by reaction of Cl_2 gas and copper under 700 °C in ~~a~~ closed system.
$2Cu + Cl_2 (g) \rightarrow 2CuCl$ (a reaction temperature: 700 °C)
Above two raw materials are transferred to a reactor through a hoist and the reacted material is cooled. After auto-pulverizing, the products are packed and sealed up and sent out goods.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (16)

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Exposure limit value
Type : OSHA PEL (8-hour TWA)
Value : Fume (Cu): 0.1 mg/m^3
Dusts and mists (as Cu): 1.0 mg/m^3
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
22.07.2005 (22)

Exposure limit value
Type : ACGIH TLV (8-hour TWA)
Value : Fume (Cu): 0.2 mg/m^3
Dusts and mists (as Cu): 1.0 mg/m^3
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (22)

Exposure limit value
Type : NIOSH *REL (10-hour TWA)
Value : Fume (as Cu): 0.1 mg/m^3
Dusts and mists (as Cu): 1.0 mg/m^3
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (22)
* REL = recommended exposure limit

Exposure limit value
Type : NIOSH *IDLH
Value : Fume, dusts, and mists (as Cu): 100 mg/m^3
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (22)
* IDLH = immediately dangerous to life and health

Exposure limit value
Type : OEL (8-hour TWA) – Korea
Value : Fume (as Cu): 0.1 mg/m^3
Dusts and mists (as Cu): 1.0 mg/m^3
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (24)

1.9 SOURCE OF EXPOSURE

Source : Environment
Remarks : Copper monochloride is ~~e~~occurred in nature as the mineral nantokite.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data

Flag : Critical study for SIDS endpoint
22.07.2005 (2)

Source : Production and processing
Remarks : In Korea, one company produces copper monochloride. In the production facilities, copper monochloride is produced in a closed system and may be emitted to air and water. In the manufacturing process, wastewater containing copper ions is reused in the production of copper dichloride. After production of copper dichloride, sewage is treated in the facilities and is discharged to wastewater treatment plant. The measured concentration of copper in treated sewage was approximately 2 mg/L. This wastewater is transferred into the municipal sewage treatment plant. It is emitted into the river and copper concentration discharged wastewater is not detected. In the stack of the factory, filtered dust is emitted to the atmosphere. Measured concentration of copper in the exhaust gas was approximately 4 mg/m^3.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
22.07.2005 (16)

Source : Human exposure by production and processing
Remarks : In the production facility, workers have a potential exposure to dust of copper monochloride in a packing area where local ventilation systems are placed concurrently with general ventilation systems. The 8hr-TWA concentration of dust was ranged from 0.6 to 0.9 mg/m^3, which is below the occupational exposure limit of 10 mg/m^3.

When workers put the raw materials including copper monochloride into a reactor in the dye manufacturing, the negative pressure of the reactor reduced dust exposure. According to the monitoring data, air concentration levels of dust for workplace were approximately 0.5 mg/m^3, in the case of copper ranging from N.D. to 0.0007 mg/m^3. These values were less than the occupational exposure limit of 10 mg/m^3 as total dust and 1 mg/m^3 as Cu, respectively.
There are no monitoring data available in a CO or H_2 manufacturing plant where a small amount of copper monochloride was used as a catalyst.

The following controls are being applied in all facilities: engineering controls; administration controls such as regulation of industrial safety and health and safe work practices within a company; and the use of personal protective equipment (PPE) such as dust masks, gloves, and protective clothing.
Reliability : (2) Reliable with restrictions
2g – Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
22.07.2005 (16)

1.10 ADDITIONAL REMARKS

Memo : Regulations and Guidelines Applicable to Copper

Remark :

Table. Regulations and Guidelines Applicable to Copper

Agency	Description	Information	Reference
NATIONAL Regulations and Guidelines:			
a. Air			
EPA	Serious health effects form ambient air exposure (Cu)		EPA 2002b 40CFR1910.1000
b. Water			
DOT	Marine pollutant (Cu metal powder and copper sulfate)		DOT 2002 49 CFR172.101, Appendix B
EPA	Drinking water standard Action level (Cu) MCLG (Cu)	 mg/L 1.3 mg/L	EPA 2002c EPA 2002d 40CFR141.51(b)
	Groundwater monitoring (Cu) Suggested method 6010 7210	 PQL 60 µg/L 200 µg/L	EPA 2002g 40CFR264, Appendix IX
	Water quality criteria (Cu) Fresh water CMC CCC Salt water CMC CCC Human health for consumption of water and organism Organoleptic effect criteria	 13.0 µg/L 9.0 µg/L 4.8 µg/L 3.1 µg/L 1,300 µg/L 1,000 µg/L	EPA 1999
c. Food and Drugs			
FDA	Bottled water; allowable level (Cu)	1.0 mg/L	FDA 2001a 21CFR165.110
IOM	Recommended dietary allowance (RDA) Tolerable upper intake level	0.9 mg/day 10 mg/day	IOM 2001
d. Other			
EPA	Carcinogenicity classification (Cu) RfC RfD	Group D[b] No data No data	IRIS 2004
	Reportable quantity designated as a CERCLA hazardous substance under Section 307(a) of the Clean Water Act (Cu)	5,000 pounds	EPA 2002h 40CFR302.4
	Reportable quantity designated as a CERCLA hazardous substance under Section 311(b) (4) of the Clean Water	10 pounds	EPA 2002h 40CFR302.4

	Act (copper sulfate)		
STATE Regulations and Guidelines			
a. Air			
lllinois	Toxic air contaminant (Cu)		BNA 2001
Louisiana	Toxic air pollutant[C] Minimum emission rate (Cu and compounds)	 25 pounds/year	BNA 2001
New Mexico	Toxic air pollutant Fume (Cu) OEL Emissions Dusts and mists (as Cu) OEL Emissions	 0.2 mg/m^3 0.0133 pounds/hour 1.0 mg/m^3 0.0667 pounds/hour	BNA 2001
Vermont	Cu compounds Hazardous ambient air standard Averaging time Action level	 100 µg/m^3 8 hours 4 pounds/hour	
b. Water			
Arizona	Drinking water guideline (Cu)	1,300 µg/L	HSDB 2004
North Carolina	Groundwater quality standard (Cu)	1.0 mg/L	BNA 2001
c. Food	No data		
d. Other			
Arizona	Soil remediation levels (Cu and compounds) Residential Non-residential	 2,800 mg/kg 63,000 mg/kg	
Florida	Toxic substance in the workplace (Cu fume, dust, and mist)		BNA 2001

[b]Group D: not classifiable as to human carcinogenicity

BNA = Bureau of National Affairs; CERCLA = Comprehensive Environmental Response Compensation and Liability Act; CFR = Code of Federal Regulations; CCC = criterion continuous concentration; CMC = criteria maximum concentraion; DOT = Department of Transportation; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous substances Data Bank; IARC = International Agency for Research on Cancer; IOM = Institute of Occupational Medicine; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; OEL = occupational exposure limit; PQL = practical quantitation limits; RDA = recommended dietary allowance; RfC = inhalation reference concentration; RfD = oral reference dose

Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (22)

Memo : Regulations and Guidelines Applicable to Copper in Korea

Remark :

	Information
a. Air an emission standard	10 mg/m^3
b. Water an effluent standard Drinking water standard	< 3 mg/ł L 1 mg/ł L

Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (16)

1.11 LAST LITERATURE SEARCH

1.12 REVIEWS

2.1 MELTING POINT

Value : 430 °C
Remarks :
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
22.07.2005 (2), (7), (8)

2.2 BOILING POINT

Value : 1,400 °C
Decomposition :
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
22.07.2005 (8)

Value : 1,490 °C
Decomposition :
Reliability : (4) Not assignable
4b - Secondary literature
22.07.2005 (7)

2.3 DENSITY

Type : Density
Value : 4.14 g/cm^3
Temperature : 25 °C
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
22.07.2005 (2)

Type : Density
Value : 4.14 g/cm^3
Temperature :
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (8)

Type : Density
Value : 3.53 g/cm^3
Temperature :
Reliability : (4) Not assignable
4b - Secondary literature
22.07.2005 (7)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : 1 mmHg
Temperature : 546 °C
Reliability : (4) Not assignable
4b - Secondary literature
22.07.2005 (7)

2.5 PARTITION COEFFICIENT

Remarks : Not applicable; inorganic salt
22.07.2005

2.6.1 WATER SOLUBILITY

Value : 47 mg/L
Temperature : 20 °C
Remarks :
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
22.07.2005 (8)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

Remark : Solutions oxidize rapidly in air
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
22.07.2005 (2)

2.12 DISSOCIATION CONSTANT

Remark : $Cu^{+} + Cl^{-} = CuCl_{(aq)}$
Log ß = 3.0±0.1 (at 25 °C)
Reliability : (2) Reliable with restrictions
2e - Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Flag : Critical study for SIDS endpoint
2005.11.17 (3)

Remark : Dissociation reaction of copper monochloride was calculated by regression of Helgeson-Kirkham-Flowers equations

Table. Predicted formation constants (logK) for $CuCl_{(aq)}$

T (°C)	$Cu^{+} + Cl^{-} = CuCl_{(aq)}$									
	0.5 kb	1 kb	1.5 kb	2 kb	2.5 kb	3 kb	3.5 kb	4 kb	4.5 kb	5 kb
100	3.75	3.70	3.66	3.63	3.61	3.59	3.58	3.57	3.57	3.57
200	3.68	3.58	3.51	3.45	3.40	3.36	3.33	3.30	3.28	3.26
300	3.96	3.74	3.60	3.48	3.40	3.32	3.26	3.21	3.17	3.13
400	4.72	4.16	3.88	3.68	3.52	3.40	3.30	3.22	3.15	3.09
500		5.00	4.37	4.02	3.77	3.58	3.43	3.31	3.20	3.12
600		6.36	5.09	4.50	4.13	3.85	3.64	3.47	3.33	3.21
700			5.86	5.08	4.57	4.20	3.92	3.70	3.52	3.37
800				5.63	5.04	4.59	4.25	3.98	3.77	3.59

900				6.11	5.48	4.99	4.60	4.29	4.06	3.87
1000					5.85	5.33	4.91	4.60	4.36	4.18

Reliability : (2) Reliable with restrictions
2e - Study well documented, meets generally accepted scientific principles, acceptable for assessment.
2005.11.17 (9)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Remark : Cu (II) + e -> Cu (I) E=0.159
Cu (I) + e -> Cu (0) E=0.520
Cu (II) + 2e -> Cu (0) E=0.340
Reliability : (4) Not assignable
4c - Original reference not available
2005.11.17 (1)

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

Remarks : The copper (I) ion is unstable in aqueous solution, tending to disproportionate to copper (II) and copper metal unless a stabilizing legend is present. The copper (I) compounds stable in water are insoluble ones such as the sulfide, cyanide and fluoride.
Reliability : (2) Reliable with restrictions
2g - Data from handbook or collection of data
Flag : Critical study for SIDS endpoint
2.07.2005 (23)

3.1.3 STABILITY IN SOIL

3.2.1. MONITORING DATA

3.2.2 FIELD STUDIES

Type of measurement :
Media :
22.07.2005

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : Oether
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year :
Remarks :
22.07.2005

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Remarks : Not applicable; inorganic salt
22.07.2005

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type : Static
Species : *Oryzias latipes*
Exposure period : 96 hours
Unit : mg/L
Analytical monitoring : Yes
LC_{50} : 0.039
Method : OECD TG 203 "Fish, Acute Toxicity Test"
Year : 2005
GLP : Yes
Test substance : Other TS: Copper monochloride (CuCl), purity = 97 %
Sigma-Aldrich Corporation, Lot. No. 14014JB
Test conditions : - *Test organisms*
Length: 2.7 ± 0.1 cm
Weight: 0.16 ± 0.01 g
Loading: 5.0 L of the test solution in 8.7 L aquarium per 7 fish
Pretreatment: Fish were acclimated for 7 days before test. No food was fed before 1 day and during the test period.
- *Test conditions*
Dilution water source: Tap water passed through activated carbon and a membrane filter (1 μm).
Water chemistry: DO: 6.3 - 8.8 mg/L (75 - 105 %), pH: 7.28 - 7.89, hardness: 25.4 mg/L as $CaCO_3$, alkalinity: 26.1 mg/L as $CaCO_3$,
Temperature: 24.0 ± 0.2 °C
Light: 800 - 1,070 Lux, Light periodicity: 16/8 (light/dark)
A group of 7 fish was used without duplication. DMSO was used as a solvent control and its concentration was 100 mg/L. Copper concentrations were analyzed with ICP-AES. The LC_{50} value and 95 % confidence limits were calculated by moving average angle method (EPA/600/4-85/013, 1985).
Remarks : The mean measured concentrations were 17.0, 19.3 and 24.6 % of nominal concentration at 48 hrs and 32.0, 29.3, 20.8 % at 96 hrs. The measured concentrations remained 100.0, 100.0, and 164.0 % of initial concentrations in the middle of the test and 188.2, 151.8, 138.7 % at the end of the test. The ion strength of test solution at the end of test became higher than the initial of the test due to being other ions resulted from accumulation of bio-contaminant like feces of the test organism. The measured concentrations of copper were increased due to existence of other ions in the test solution.
Result : Test concentrations were as follows;
Nominal concentration: control, solvent control, 0.1, 0.15, 0.24, 0.39, 0.63, 1 mg/L
Mean measured concentration: control, solvent control, 0.021, 0.033, 0.047, 0.047, 0.137, 0.236 mg/L

Table. Acute toxicity test results for copper monochloride of *Oryzias latipes* (Unit; mg/L)

Exposure time	24 hrs	48 hrs	72 hrs	96 hrs
LC_{50}	0.16	0.044	0.039	0.039
95 % confidence limits	0.13 ~ 0.23	0.039 ~ 0.049	0.032 ~ 0.048	0.032 ~ 0.048
Highest test concentration resulting in 0 % mortality	0.047	0.033	0.021	0.021
Lowest test concentration resulting in 100 % mortality	-	0.047	0.047	0.047
No-observed effect level	0.033	0.033	0.021	0.021

Table. Cumulative mortality of *Oryzias latipes*

Nominal	Mean	Number of	Cumulative number of dead fish

concentrations (mg/L)	measured concentrations (mg/L)	organisms tested	24 hrs	48 hrs	72 hrs	96 hrs
Control	Control	7	0	0	0	0
Solvent Control	Solvent Control	7	0	0	0	0
0.1	0.021	7	0	0	0	0
0.15	0.033	7	0	0	1	1
0.24	0.047	7	0	6	6	6
0.39	0.047	7	1	7	7	7
0.63	0.137	7	1	7	7	7
1	0.236	7	6	7	7	7

Reliability : (1) Reliable without restrictions
1a - GLP guideline study
Flag : Critical study for SIDS endpoint
22.07.2005 (19)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : Static
Species : *Daphnia magna*
Exposure period : 48 hours
Unit : mg/L
EC_{50} : 0.25 mg/L
Analytical monitoring : Yes
Method : OECD TG 202, "*Daphnia sp*., Acute Immobilisation Test and Reproduction Test"
Year : 2003
GLP : Yes
Test substance : Other TS: Copper monochloride (CuCl), purity = 97 %
Sigma-Aldrich Corporation, Lot. No. 17119BO
Test conditions : - *Test organisms*
Age: Juveniles within 24 hours old
Supplier: GSF Institute of Ecological Chemistry, Germany
- *Test conditions*
Dilution water source: OECD M4 medium, hardness: 243 mg/L as $CaCO_3$, alkalinity: 42 mg/L as $CaCO_3$
Water chemistry: DO: 8.7 - 9.4 mg/L (96 - 103 %), pH: 7.85 - 8.02
Temperature: 20.1 ± 0.4 °C
Light: 598 - 632 Lux, Light periodicity: 16/8 (light/dark)
3 replicates per 10 organisms were used. Copper concentrations were analyzed with ICP-AES. The EC_{50} value and 95 % confidence limits were calculated by moving average angle method (EPA/600/4-85/013, 1985).
Remark : The stability test at 1.03 mg/L of copper monochloride in OECD M4 medium was studied. During 48 hrs the substance was remained 74.9 to 74.1 %.
In the confirmation test, the mean measured concentrations were 34.5, 51.7, and 68.2 % of nominal concentrations at 48 hrs. The measured concentrations remained 50.4, 68.8, and 88.2 % of initial concentrations at the end of the test.
Result : Test concentrations were as follows; Nominal concentration: control, solvent control, 0.2, 0.3, 0.6, 1.0, 1.7, and 2.8 mg/L.
Mean measured concentration: control, solvent control, 0.09, 0.18, 0.42, 0.74, 1.29, and 1.98 mg/L

Table. Acute toxicity test results for copper monochloride of *Daphnia magna* (Unit; mg/L)

Exposure time	24 hrs	48 hrs
EC_{50}	0.33	0.25
95 % confidence limits	0.28 ~ 0.40	0.20 ~ 0.30
Highest test concentration resulting in 0 % mortality	-	-
Lowest test concentration resulting in 100 % mortality	0.74	0.74
No-observed effect level	-	-

Table. The results of cumulative immobilization data for *Daphnia magna*

Nominal concentrations (mg/L)	Mean measured concentrations (mg/L)	Number of organisms tested	Cumulative number of organisms immobilized	
			24 hrs	48 hrs
Control	Control	30	0	0
Solvent control	Solvent control	30	0	0
0.2	0.09	30	1	3
0.3	0.18	30	1	3
0.6	0.42	30	23	28
1.0	0.74	30	30	30
1.7	1.29	30	30	30
2.8	1.98	30	30	30

Reliability : (1) Reliable without restrictions
1a - GLP guideline study
Flag : Critical study for SIDS endpoint
22.07.2005 (18)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : *Pseudokirchneriella subcapitata*
Endpoint : Growth rate
Exposure period : 72 hours
Unit : mg/L
EC_{50} : 0.058
Analytical monitoring : Yes
Method : OECD TG 201, “Alga, Growth Inhibition Test”
Year : 2005
GLP : Yes
Test substance : Other TS: Copper monochloride, purity = 97 %
Sigma-Aldrich Corporation, Lot. No. 14014JB
Test conditions : - *Test organisms*
Laboratory culture: ATCC culture medium 625 Gorham’s medium
Strain No: ATCC 22662
Method of cultivation: sterilization
- *Test conditions*
Temperature: 23.1 °C
Dilution water source: OECD medium
Water chemistry: pH 7.65 - 8.36 at the beginning and pH 7.81 - 7.97 at the end of tests
Light level: 7,814 - 8,290 Lux
Initial cell density: 1 x 10^4 cells/mL
Test design: 3 replicates
The sterile medium and DMSO were used for the control and solvent control, respectively. The concentration of organic solvent was 67 mg/L. Copper concentrations were analyzed with ICP-AES. The EC_{50} ~~value~~ and NOECs were calculated by Linear interpolation, Tidepool Scientific Software (TOXCALC Version 5.0.12) and Dunnett’s test, respectively.
Remarks : The concentrations of test substance were analyzed in control, solvent control, 0.0094, 0.019, 0.038, 0.075, and 0.15 mg/L of test solutions at the beginning (0 hr) and at the end (72 hrs) of the test. The concentration of

copper in the 0.0094 and 0.019 mg/L of test solution were not detected because the limit of detection (LOD) of this instrument (ICP-AES) is 0.01 mg/L. Nominal concentrations were 0.038, 0.075 and 0.15 mg/L and measured concentrations were 0.0368, 0.0525 and 0.0624 mg/L above the detection limit. The measured concentrations remained 41.6 - 91.8 % of the nominal concentrations.

Result : Some test solutions could not analyzed because the concentrations of them were under the LOD so all results were expressed as nominal concentration.
Nominal concentration: Control, Solvent control, 0.0094, 0.019, 0.038, 0.075, and 0.15 mg/L

Table. Test results for copper monochloride of *Selenastrum capricornutum* during 72 hrs (Unit; mg/L)

Endpoint values	Growth rate	Biomass
EC_{50}	0.058	0.057
95 % confidence limits	0.051 ~ 0.066	0.052 ~ 0.057
No-observed effect concentration (NOEC)	0.038	0.038
Lowest-observed effect concentration (LOEC)	0.075	0.075

Table. Cell density of *Selenastrum capricornutum* (ATCC 22662) during the test

Nominal Concentrations (mg/L)	Cell density (x 10^4 cell/mL)			
	0 hr	24 hrs	48 hrs	72 hrs
Control	6.7×10^3	1.4×10^4	1.6×10^5	7.3×10^5
Solvent control	6.4×10^3	7.9×10^3	8.8×10^4	6.3×10^5
0.0094	4.6×10^3	1.9×10^4	1.7×10^5	8.0×10^5
0.019	5.5×10^3	1.6×10^4	1.5×10^5	8.5×10^5
0.038	1.1×10^4	1.5×10^4	1.5×10^5	8.8×10^5
0.075	6.8×10^3	4.6×10^3	9.3×10^3	1.8×10^4
0.15	6.7×10^3	1.3×10^4	6.8×10^3	8.6×10^3

Table. Percent inhibition of growth rates per concentration

Nominal Concentrations (mg/L)	Growth rates		
	Growth rate	Relative growth rates (%)	Relative inhibition (%)
Control	0.066	-	-
Solvent control	0.064	98	2
0.0094	0.073	111	-11
0.019	0.070	107	-7
0.038	0.063	95	5
0.075	0.009	14	86
0.15	0.003	4	96

Nominal Concentrations (mg/L)	Areas under the curve		
	Areas under the curve	Relative growth rates (%)	Relative inhibition (%)
Control	12566000	-	-
Solvent control	488400	76	24
0.0094	13860000	110	-10
0.019	13856000	110	-10
0.038	13816000	110	-10
0.075	139200	1	99
0.15	167600	1	99

Reliability : (1) Reliable without restrictions
1a – GLP guideline study

Flag : Critical study for SIDS endpoint
22.07.2005 (13)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1 ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD_{50}
Species/strain	:	Rat / Sprague-Dawley
Sex	:	Male and Female
No. of animals	:	Male 5 and Female 25
Route of Administration	:	Dermal route
Exposure time	:	24 hours
Dose	:	2,000 mg/kg bw for males 2,000 mg/kg bw, 1,500 mg/kg bw, 1,000 mg/kg bw, and 500 mg/kg bw for females
Value	:	> 2,000 mg/kg bw for males, 1,224 mg/kg bw for females
Method	:	OECD Test Guideline 402 “Acute dermal toxicity”
Method remarks	:	- *Preparation of test substance* In this study, the test substance was weighed and wetted with a saline solution. - *Treatment procedure* At first, the limit tests at one dose level of 2,000 mg/kg bw were performed. - *Administration of the test substance* Animals were clipped their fur on dorsal part approximately 10 % of the total body surface area one day before dosing. The test substance was applied uniformly and held in contact with the skin with a porous gauze dressing and non-irritating tape for 24 hours. At the end of the exposure period, residual test substance was removed using a saline solution. - *Clinical observations* Cages of rats were checked at least once a day for any mortality. Animals were individually observed hourly during the first 4 hours after dosing with special attention, and daily for a total of 14 days. The nature and severity of the clinical signs and time were recorded at each observation. - *Body weights* The body weight of each rat was recorded on day 1 (prior to dosing), day 8 and day 15 (prior to necropsy). Individual body weight changes were calculated. - *Necropsy* All animals were killed on day 15 by carbon dioxide asphyxiation and subject to a gross necropsy. All gross pathological changes were recorded for each animal. Microscopic examination was not conducted because evidence of gross pathlogical changes was not showed.
Year	:	2003
GLP	:	Yes
Test substance	:	Other TS: Copper monochloride, purity = 97 %, Simga-Aldrich corporation, Lot No. 17119BO
Test conditions	:	- *Body weight of test animals during the study*: 255.3 g for males and 216.6 - 225.0 g for females - *Dose per time period*: single treatment - *Post dose observation period*: 14 days

Results : - *Mortality and clinical signs*
During the study, males showed no death, but females showed 4 deaths in 2,000 mg/kg bw, 4 deaths in 1,500 mg/kg bw, and 1 death in 1,000 mg/kg bw, respectively. It was observed that symptom of the hardness of skin, an exudation of hardness site, formation of scar/falling off scar, and reddish change in application sites. It was considered to relate with application of test substance.
A reddish or black urine was observed in 2,000, 1,500, and 1,000 mg/kg bw of female, and a paleness was observed in 2,000 mg/kg bw of female. This sign was considered as a symptom caused by systemic toxicity. Test article absorbed through dermal appeared to bring about hemolysis of blood cell.
- *Body weights*
All males gained normal body weight throughout the study. In comparison with the control (no treated control) the female showed noticeable loss of body weight on day 8 in 1,500 mg/kg bw, but one of rats given to 1,500 mg/kg bw was found to be moribund rat.

- *Gross pathology*
In macroscopic examination, on application sites, the died males showed hardness of skin and acute rats showed necrosis and hemorrhage in subcutaneous. At test finished, it was observed crust of applied site in necropsyp rat. The higher dose concentration, this symptom was severely observed. It was found to be appeared inflammatory response of applied site caused by test substance and toxicity by it. Internally, no abnormality was observed in all animals. In 1,500 mg/kg bw of 1 female, size of kidney, adrenal gland and spleen were enlarged and lung became smaller, but it was not considered test substance's effect but lesion showed in rodent.

Table. Mortality and clinical signs

Group	Animal No.	Hours after treatment on Day1				Days after treatment													Mortality (%)
		1	2	3	4	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
T1	M1	N	Nd	Nd	Nd	Nd	Ha,H,R	Ha, H, R	Ha,R	Ha,R	Ha,R, Sc	Ps	Ps	Ps	Sc	Sc	Sc	Sc	Sc	0/5 (0)
	M2	H	H	N	N	Nd, Ha	Ha,H,R	Ha,H,R	Es, Ps	Es,Ps	Es,Ps	Es	Es	Es	Sc	Sc	Sc	Sc	Sc	
	M3	H	H	N	N	Nd, Ha	Ha, H	Ha,H, R,Cp	Es, Ps	Es,Ps	Es, Ps	Es, Ps	Es, Ps	Es, Ps	Es, Ps	Es, Ps	Es, Ps	Es ,Ps	Es ,Ps	
	M4	H	H	N	N	Nd, Ha	Ha,Nd ,Cp,le	Ha,R, H,Cp	R,Ps	R,Ps	Es,Ps	Es, Ps	Es, Ps	Es, Ps	Es, Ps	Es, Sc	Es, Sc	Es ,Sc	Es ,Sc	
	M5	H	H	Nd	Nd	Ha	Ha,H, R	Ha,H,R	R,Es	R,Es, Ps	Es,Ps	Es	Es	Es	Sc	Sc	Sc	Sc	Sc	
T1	F6	N	H	N	N	Ha,H ,Nd	H,Ha, Pa,Ru	Ha,H,Pa,R	Es,R	Es,R, Ha	Ps,Es	Ps,Es	Ps, Es	Ps, Es	Ps, Es	Ps, Es	Ps, Es	Ps ,Es	Ps ,Es	4/5 (80) -
	F7	N	N	N	N	Ha,H ,Bu	H,Ha, Pa,Nf, R,le,Ru	H,Cp,Ha,R,De, Nd,Pa, Ru	MH	-	-	-	-	-	-	-	-	-	-	
	F8	H	H	N	N	Ha,H ,Nd	H,Ha, De,Pa, Nf,Bu	Cp,Ha, R, le,De,Nd,Pa,Ru	FD	-	-	-	-	-	-	-	-	-	-	
	F9	N	H	N	N	Ha,H ,Bu	H,Ha, Nf,R,le,Pa,Bu	le,Ha,R, Pa,Nd,Cp	FD	-	-	-	-	-	-	-	-	-	-	
	F10	H	H	Nd	Nd	Ha,H ,Nd, Bu	H,Ha, Nf,R, Ru, Pa,Bs	Ha,R,le, Nd,De, Pa	MH	-	-	-	-	-	-	-	-	-	-	

T2	F11	H	H	H	H	Ru,Nd,De,Dg,Ha,H,Sh	Rh,Ru,De,Nd,H,Ha	De,Dm,Dg,Nd,H,Rh,Ha	De,Dg,Nd,H,Rh,Ha	De,Dg,Nd,H,Rh,Ha,Hs,E	De,Dg,Nd,H,Rh,Ha,Sh	De,Dg,Nd,H,Rh,Ha,E,MH	-	-	-	-	-	-	-	4/5 (80)
	F12	H,Nd	H,Nd	H,Nd	H,Nd	Ru,P,Ct,le,Ha,H	FD	-	-	-	-	-	-	-	-	-	-	-	-	
	F13	H	H	H	H	Nd,Wg,Ha,H	Rh,H,Ha	Ha	Ha	Ha	Ha	Hg	Hg	Sc	Sc	Sc	Sc	Sc	Sc	
	F14	H,Nd	H,Nd,le	H,Nd	H,Nd,le	Ru,Nd,Ha,H	Rh,H,Ha	Ha	Ha,H,Rh,P	Ha,H,Rh,P,Dg,E	FD	-	-	-	-	-	-	-	-	
	F15	H	H	H	H	Ru,Wg,Ha,H	Rh,H,Ha,Wg	Ha,Dg	Ha,Rh,Dg,Pp	FD	-	-	-	-	-	-	-	-	-	
T3	F16	H	H,Sh	H	H	Ru,P,Ha,H	Ru,H,Nd	Nd,Dg,H,Ha	Nd,Dg,H,Ha,E	Nd,Dg,Dm,H,Rh,Ha,E,Dy	FD	-	-	-	-	-	-	-	-	1/5 (20)
	F17	Nd	Nd,H	Nd,H	Nd,H	De,Nd,Ha,H	H,Ha,Nd	Ha,H	Ha	Ha	Ha,Ps	Ua	Hg	Hg	Hg	Hg	Hg	Hg	Hg	
	F18	Nd	Nd,H	Nd,H	Nd,H	Ru,Nd,Ha,H	H,Ha	H,Ha,Nd	Ha	Ha	Ha	Ha	Ha	Ha	Ps	Ps,Hg	Ps,Hg	Hg	Hg	
	F19	H	H,Ss	H	H	H,Ha	H,Ha	H,Ha	Ha	Ha	Ha,Ps	Ha,Ps	Ha	Ha	Sc	Sc	Sc	Ps	Ps	
	F20	H	H	H,Sh	H	H,Ha	H,Ha	H,Ha	Ha	Ha	Ha	Ha,Ps	Ps,Ha	Ps	Ps,Hg	Hg	Hg	Hg	Hg	

T4	F21	Nd	Nd, H	Nd, H	Nd, H	Ha, H	Ha,H	Ha,H	Ha	Ha	Ha	N	N	N	N	N	N	N	N	0/5 (0)
	F22	Nd	H	H	H	Ha, H	Ha,H	Ha	Ha	Ha	Ha	Ps	Ps	Ps	Ps	Ps, Es	Ps, Es	Es	Es	
	F23	N	N	H	H	Ha, H	Ha,H	Ha	Ha	Ha	Ha	Ha	Ha	Ha	Ha	Ha	Ha	Hg	Hg	
	F24	Nd	Nd, H	Nd, H	Nd, H	Ha, H	Ha,H	Ha	Ha	Ha	Ha	Ps	Ps	Ps	Ps	Ps	Ps	Es	Es	
	F25	Nd	Nd, H	Nd, H	Nd, H	Ha, H	Ha,H	Ha,H	Ha	Ha	Ha	Ps	Ps	Ps	Ps	Es	Es	Es	Es	
C	F26	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	0/5 (0)
	F27	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	F28	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	F28	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	F30	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	

T1: Treatment (2,000 mg/kg bw), T2: Treatment (1,500 mg/kg bw), T3: Treatment (1,000 mg/kg bw), T4: Treatment (500 mg/kg bw), C: No treated control
M: Male, F: Female
Bs: Black stool; Bu: Black urine; Cp: Crouch position; Ct: Cool to touch; De: Discharge around eyes; Dg: Dirty fur around genital track; Dm: Discharge around mouth; Dy: Dyspnea; E: Emaciation; Es: Exudation in application site; FD: Found dead; H: Hypoactivity; Ha: Hardness on application site; Hg: Hemorrhage in application site; Hs: Hypersensitive; Ie: Incomplete eyelid opening; MH: Moribund and humanly sacrificed; N: Normal; Nd: Nasal discharge (reddish); Nf: No evidence of food consumption; P: Piloerection; Pa: Pale; Pp: Prone position; Ps: Progression of falling scar; R: Reddish change in application site; Rh: Roughened hair coat; Ru: Reddish urine; Sc: Scar in application site; Sh: Standing haunch; Ss: Soft stool; Ua: Ulceration in application site; Wg: Wet fur around genital track
-: Not applicable

Table. Summary of group mean body weights

Sex	Group	Group mean bodyweight (mean ± S.D., g)		
		Day 1	Day 8	Day 15
Male	T1	255.4 ± 4.66	277.3 ± 11.89	325.4 ± 13.37
Female	T1	225.0 ± 7.66	-	-
	T2	220.6 ± 11.30	191.2 * ± 37.41	-
	T3	223.3 ± 11.01	231.6 ± 11.26	243.4 ± 13.82
	T4	221.9 ± 11.48	234.1 ± 11.07	244.4 ± 13.88
	C	216.6 ± 6.83	227.6 ± 6.39	240.3 ± 8.48

T1: 2,000 mg/kg bw; T2: 1,500 mg/kg bw; T3: 1,000 mg/kg bw; T4: 500 mg/kg bw; C: No treated control;
*: Significantly different compared to no treated control group, $p < 0.05$

Table. Gross necropsy findings (Group summary)

Group	T1	T1	T2	T3	T4	C
Sex	Male	Female				
Number of animals examined	5	5	5	5	5	5
External						
No gross findings			1	1	2	5
Hair loss and hemorrhage in application site	2					
Hair loss, exudation, and falling off scar in application site	3	1				
Perioral discharge		4	4	1		

Perianal discharge		4				
Necrosis in application site	2	5	4	1		
Perianal contamination			4	1		
Hardness in application site			3	1		
Scar on applied site				3	3	
Internal						
No gross findings	2		1	4	5	5
Hemorrhage in subcutaneous	3	1				
Adrenal gland (left) – enlarged			1			
Kidney (both) – enlarged, brownish green, mottled			1			
Spleen – enlarged, dark red			1			
Lung – small			1			
– hemorrhagel			1			
Hydrothorax			1			
Autolysis		4	1			
Severe autolysis			2	1		

Conclusions : When given copper monochloride to rats by dermal, it was found to cause skin inflammation and injury. In case of being absorbed by dermal, it was found to cause systemic toxicity symptom. Female rats appeared to be more susceptible to copper monochloride than males based on mortality and clinical signs.
The acute lethal dose (LD_{50}) of copper monochhoride was ≥2,000 mg/kg bw for males and 1,224 mg/kg bw ~~to~~ for females. In case of females, 95 % confidence limits were 1,032 ~ 1,453 mg/kg bw.

Reliability : (1) Reliable without restriction
1a – GLP guideline study (OECD)

Flag : Critical study for SIDS endpoint
22.07.2005 (17)

5.1.4 ACUTE TOXICITY BY OTHER ROUTES OF ADMINISTRATION

5.3 CORROSIVENESS/IRRITATION

5.4 SKIN SENSITISATION

5.5 REPEATED DOSE TOXICITY

Species/strains : Rat / Sprague-Dawley
Sex : Male/Female
Route of administration : Oral (Gavage)
Method : OECD TG 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year : 2004
GLP : Yes
Test substance : Other TS: Copper monochloride; purity = 97 %; Sigma-Aldrich Corporation; LOT No. 17119BO
Dose levels : 0, 1.3, 5, 20, and 80 mg/kg bw/day
Exposure period : 30 days for males and 39 to 51 days for females
Frequency of treatment : Daily
Control groups : Yes (Concurrent no treatment)
Post exposure observation period : No

Statistical methods : If the variance was homogenous, the data were subjected to one-way ANOVA. Otherwise, they were analyzed by the Kruskal-Wallis nonparametric ANOVA. If either of these tests showed statistical significance, the data were analyzed by the multiple comparison procedure of Dunnett of Scheffe to compare the treated groups with the controls. Clinical signs and gross findings were presented as frequencies, and they were analyzed by χ^2-test followed by the Fisher's exact test where necessary. A statistical difference was observed at $p < 0.05$ or $p < 0.01$.

Test conditions : **Test organism**
- Sex: male/female
- Age at study initiation: 7-week-old animals
- Body weights at study initiation: 297.0 - 369.6 g for males and 180.3 - 222.3 g for females
- No. of animals per sex per dose: 12

Method remarks : **Observation of F0**
- *Clinical signs*: Clinical signs including mortality, moribundity, general appearance, and behavior changes were observed once a day after dosing the animals during the study period.
- *Functional observation tests*: Functional observation tests such as right reflex, traction test, pupil reflex, auditory reflex, and negative geotaxis were performed on 5 animals of each group at the end of dosing date.
- *Body weights*: The body weights were measured once a week during the pre-mating period, but for pregnant females they were measured on day 0, 7, 14, 20 of gestation period, within 24 hrs of parturition and day 4 of postpartum.
- *Food consumption*: Food consumption was measured once a week during pre-mating period. It was measured measured on day 1, 8, 15 and 21 of gestation and on day 1 and 4 of lactation.
- *Urinalysis*: Five males and five females were selected from each test group. Following seven items were tested; color, specific gravity, pH, glucose, protein, ketone body, occult blood, bilirubin, urobilinogen, nitrite, and urine sediment.
- *Hematological test*: Five male and five females from each test group were fasted for one night before necropsy. Animals were anesthetized with ether and the abdomen was cut open to collect blood. Following 17 items were measured; white blood cell count (WBC), red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (PLT), differential leukocyte count (neutrophil (NEU), lymphocyte (LYM), monocyte (Mono), eosinophil (EOS), basophil (BAS), and large unstained cells (LUC)), reticulocyte count (RET), prothrombin time (PT) and met-hemoglobin (Mhgb).
- *Biochemical test:* Following 18 items were measured: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate (ALP), glucose (GLU), total protein (TP), albumin (ALB), Albumin/globulin ratio (A/G), blood urea nitrogen (BUN), creatinine (CREA), total cholesterol (TCHO), total bilirubin (TBIL), triglyceride (TG), phospholipid (PL), calcium (Ca), inorganic phosphorus (P), sodium (Na), potassium (K), and chloride (Cl).
- *Gross findings*: All adult animals were subjected to a detailed gross necropsy, which includes careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities including their contents. The following organs were weighed: brain, pituitary gland, thymus, lung, heart, liver, spleen, kidneys, adrenal glands, thyroid glands, and salivary gland.
- *Histopathological examination*: Following organs of the selected animals in the high dose groups and the controls were preserved in 10 % buffered formalin solution: brain, spinal cord, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, kidney, adrenal glands, spleen, heart, thymus,

thyroid glands, trachea, lungs, pituitary gland, intestinal lymph node, mandibular lymph node, sciatic nerve, skeletal muscle, bone marrow (femur), sternum, salivary gland, esophagus, tongue, aorta, and pancreas. Examination of the spleen, stomach, and femur was extended to the other dose groups.

NOAEL : 5 mg/kg bw/day for males, 1.3 mg/kg bw/day for females

Results : **Results for F0**

- *Mortality*: No death was observed for male rats. Three animals were dead and treatment-related death was found in one of the 80 mg/kg bw/day female group on day 1 of administration.
- *Clinical signs (Table 1, 2 & 3)*: Treatment-related clinical sign such as anemia was observed in one female of the 80 mg/kg bw/day group because the symptom was consistent with anemic signs of hematological examination. The other sings observed each sex were not considered to be affected by the test substance due to low incidence and no abnormal findings in histopathological examination.
- *Functional observation tests*: No specific results were observed in righting reflex, papillary reflex and acoustic startle response. In the negative geotaxis test, 2 males and 1 female of the control and 20 mg/kg bw/day group, respectively, did not pass the test. Two animals failed in the traction test in each treatment group except for the female control.
- *Body weights and food consumption:* There were no dose-related changes in all treatment groups.
- *Urinalysis for males*: There were no treatment-related changes.
- *Hematological test (Table 4):* There were statistical decreases on RBC, HGB, HCT, MCV, and MCH, and increases on WBC and PLT in the 80 mg/kg bw/day male groups. In the same group, neutrophil was increased compared with the controls. These findings were consistent with the hematological results observed in microcytic hypochromic anemia, also considered to be the primary cause of bone marrow hyperplasia of femur. For females, a statistically significant decrease on MCH and an increase on PLT were observed in the 80 mg/kg bw/day group. These findings were similar to those of males, but other values were different from those of males due to a sexual difference.
- *Biochemical test:* For males, a statistically significant decrease on TP and TBIL, and an increase on A/G ratio were observed in 80 mg/kg bw/day group. TBIL of the 1.3 mg/kg bw/day group was statistically increased compared with the controls. There was a decrease on K in the 1.3 and 5 mg/kg bw/day. There were no statistical differences in female groups.
- *Gross findings*: Paleness of kidney was found in 80 mg/kg bw/day male group. There was one male showing luminal gas and contents in ileum, cecum and colon in the male high dose group. No abnormal organs were observed in all females. Dead females of the 80 mg/kg bw/day group showed dark-red discoloration of lung, thoracic fluid, foamy trachea and lung, and black discoloration of stomach. They were observed in 2, 2, 1 and 1 females, respectively.
- *Organ weights*: For male rats, absolute organ weights of salivary gland were decreased in the 20 and 80 mg/kg bw/day groups. A statistically significant decrease in absolute organ weight was observed for thyroid gland in the 1.3 and 20 mg/kg bw/day groups.
There were no differences in relative organ weights for males and absolute and relative organ weights for females compared with the control group.
- *Histopathological findings of males (Table 5)*: Bone marrow hyperplasia of femur was found in 8 males of the 80 mg/kg bw/day group, and squamous cell hyperplasia of stomach were observed in 1, 2, 8 and 11 males in the 1.3, 5, 20 and 80 mg/kg bw/day groups, respectively. The frequency of these findings was statistically higher than the controls in the 20 and 80 mg/kg bw/day groups. These were considered to be cause by

the chemical. The other findings were considered to be incidental ones.
- *Histopathological findings of females (Table 5)*: Squamous cell hyperplasia of stomach was observed in 2, 5, 6 and 9 females in the 1.3, 5, 20 and 80 mg/kg bw/day groups, respectively. These findings of high frequency were statistically observed as compared to the controls in 5 mg/kg bw/day groups and above. Three dead females of the 80 mg/kg bw/day groups, squamous cell hyperplasia of stomach and congestion of kidney and lung were observed in 3, 3 and 1 females, respectively.

Table 1. Summary of clinical sings of male rats

Dose (mg/kg bw/day)	0	1.3	5.0	20	80
No. of animals	12	12	12	12	12
Loss of fur	2 (17 %)	0 (0 %)	0 (0 %)	1 (8 %)	2 (17 %)
Salivation	0 (0 %)	3 (25 %)	5 (42 %)	12 (100 %)	12 (100 %)
Soft stool	0 (0 %)	0 (0 %)	0 (0 %)	1 (8 %)	2 (17 %)
Diarrhea	0 (0 %)	0 (0 %)	1 (8 %)	0 (0 %)	2 (17 %)
Blackish stool	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	8 (67 %)

Table 2. Summary of clinical sings of female rats during pre- and mating period

Dose (mg/kg bw/day)	0	1.3	5.0	20	80
No. of animals	12	12	12	12	12
Loss of fur	0 (0 %)	2 (17 %)	0 (0 %)	0 (0 %)	1 (8 %)
Anemic	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (8 %)
Reddish tear	0 (0 %)	1 (8 %)	0 (0 %)	0 (0 %)	0 (0 %)
Eye discharge	0 (0 %)	1 (8 %)	0 (0 %)	0 (0 %)	0 (0 %)
Salivation	0 (0 %)	0 (0 %)	1 (8 %)	6 (50 %)	11 (92 %)
Blackish stool	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	4 (33 %)
Death	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	2 (17 %)

Table 3. Summary of clinical sings of female rats during gestation and lactation period

Dose (mg/kg bw/day)	0	1.3	5.0	20	80
No. of animals	12	12	11	12	9
Loss of fur	2 (17 %)	2 (17 %)	1 (9 %)	1 (8 %)	2 (22 %)
Crust formation	0 (0 %)	0 (0 %)	0 (0 %)	1 (8 %)	0 (0 %)
Lacrimation	0 (0 %)	1 (8 %)	0 (0 %)	0 (0 %)	0 (0 %)
Eye discharge	0 (0 %)	1 (8 %)	0 (0 %)	1 (8 %)	0 (0 %)
Salivation	0 (0 %)	0 (0 %)	0 (0 %)	8 (67 %)	9 (100 %)
Blackish stool	0 (0 %)	0 (0 %)	2 (18 %)	7 (58 %)	9 (100 %)
Death	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (8 %)

Table 4. Summary of hematological values (mean)

Sex	Male					Female				
Dose (mg/kg bw/day)	0	1.3	5	20	80	0	1.3	5	20	80
WBC (× 103/µL)	7.18	10.20	8.40	10.08	11.72†	6.07	5.74	6.66	7.37	80.0
RBC (× 106/µL)	8.09	8.33	7.80	7.89	6.05†	6.18	6.72	6.40	5.71	5.44
HGB (g/dL)	15.2	15.1	14.8	14.8	9.7†	11.8	12.5	12.3	10.8	9.6
HCT (%)	47.8	47.2	46.2	46.3	31.9†	40.7	42.5	41.5	37.2	33.8
MCV (fL)	59.0	56.7	59.3	58.7	52.2†	66.0	63.1	64.9	65.4	62.2
MCH (pg)	18.9	18.1	19.0	20.0	15.9†	19.1	18.6	19.2	18.9	17.7‡
MCHC (g/dL)	31.9	31.9	32.0	31.9	30.6	29.0	29.5	29.5	28.9	28.4
PLT (× 103/µL)	1104	1047	1055	1231	2927‡	1784	1942	1654	1966	2325†
RET (%)	2.4	2.5	2.7	2.9	4.3	8.5	7.2	8.0	9.5	4.9

Mhgb (%)	2.96	2.59	2.64	3.14	3.41	2.41	2.60	2.38	2.99	3.05
PT (sec)	14.4	14.1	14.7	14.4	14.2	13.8	13.3	13.7	13.7	13.0
NEU (%)	16.7	21.7	20.7	18.2	28.5‡	34.8	29.4	27.7	32.1	28.0
LYM (%)	78.1	73.6	73.4	76.9	67.5	62.1	67.1	69.6	64.4	68.2
MON (%)	3.1	2.8	3.2	2.7	2.7	1.6	1.5	1.2	2.1	2.4
EOS (%)	1.2	1.0	1.8	1.3	0.6	0.9	1.3	1.0	0.8	1.0
BAS (%)	0.3	0.2	0.3	0.3	0.2	0.3	0.2	0.2	0.1	0.2
LUC (%)	0.5	0.6	0.7	0.6	0.5	0.3	0.4	0.3	0.4	0.3

†: Statistical significance was observed at $p < 0.01$
‡: Statistical significance was observed at $p < 0.05$

Table 5. Summary of histopathological findings (Frequency)

Sex	Male					Female				
Dose (mg/kg bw/day)	0	1.3	5	20	80	0	1.3	5	20	80
No. of animals	12	12	12	12	12	12	12	12	12	12
Kidneys	12	0	0	0	12	12	0	0	0	12
- Tubular basophilia	4	0	0	0	4	6	0	0	0	3
- Lymphoid cell infiltration	2	0	0	0	1	4	0	0	0	1
- Congestion	0	0	0	0	0	0	0	0	0	3
Liver	12	0	0	0	12	12	0	0	0	12
- Microgranuloma	1	0	0	0	1	1	0	0	0	0
- Inflammation	0	0	0	0	1	0	0	0	0	1
Lungs	12	0	0	0	12	12	0	0	0	12
- Congestion	0	0	0	0	0	0	0	0	0	1
Spleen	12	12	12	12	12	12	12	12	12	12
- Extramedullary hematopoiesis	0	0	0	0	0	0	0	1	0	0
Stomach	12	12	12	11	12	12	12	12	11	12
- Squamous cell hyperplasia	0	1	2	8‡	11‡	0	2	5‡	6‡	9‡
Femur	12	12	12	12	12	12	12	12	12	12
- Bone marrow hyperplasia	0	0	0	0	8‡	0	0	0	0	0

‡ Statistical significance was observed at $p < 0.05$ using Fisher's exact two-tailed test
Following organs did not have remarkable results; brain, spinal cord, duodenum, jejunum, ileum, cecum, colon, rectum, adrenal glands, heart, thymus, thyroid glands, trachea, pituitary gland, intestinal lymph node, mandibular lymph node, sciatic nerve, skeletal muscle, sternum, salivary gland, esophagus, tongue, aorta, and pancreas

Conclusions : Repeated oral dosing of copper monochloride resulted in one death and an anemic status of females, microcytic hypochromic anemia, and bone marrow hyperplasia of femur of males in the 80 mg/kg bw/day group. In addition, squamous cell hyperplasia of stomach mucous membrane was observed at ≥20 mg/kg bw/day of males and at ≥5 mg/kg bw/day of females.
Reliability : Reliable without restrictions
1a - GLP guideline study (OECD)
Flag : Critical study for SIDS endpoint
22.07.2005 (12)

Species/strains : Rat / Sprague-Dawley
Sex : Female
Route of administration : Oral (drinking water)
Year : 1991
GLP : No data
Test substance : Other TS: Copper monochloride
Concentration levels : 0 and 100 CuCl mg/L demineralized water (approx. 0 and 10 Cu mg/kg bw)
Exposure period : 15, 30, or 90 days
Control groups : Yes (Concurrent no treatment); demineralized water without metal salts

Statistical methods : The mean ± SD was calculated from the corresponding individual values determined. The treatment groups were analyzed by Dunnett's test. A p-value below 0.05 was considered as significant.

Test conditions : - *Test organism*
Body weights at study initiation: 210 - 230 g
No. of animals per dose: 5

Method remarks : *Observation of Test animals*
The water was renewed twice each week. After 15, 30 or 90 days of treatment the livers of the animals were removed for the determination of GST (glutathione S-transferases) activity. GST catalize the metabolism of reactive substances of exogenous or endogenous. During the 90 day experiment the rats were weighed once a week and changes of body weight were calculated. The intake of food and drinking water was determined weekly.

Preparation
The liver removed were minced and homogenized in buffer (pH 7.35) and then ultra-centrifuged. The supernatant containing soluble GST was separated and used as enzyme preparation to investigate GSH S-epoxide transferase with styrene oxide as substrate and GSH S-aryltransferase with 1-chloro-2, 4-dinitrobenzene as substrate. GST was divided into two isoenzymes; GSH S-epoxide transferase (10 % of total GST activity) and GSH S-aryltransferase (90 % of total GST activity). The activity of GST was determined colorimetrically (412 nm) using each substrate.

Results : Activity of GSH S-epoxide transferase was significantly inhibited after day 15 (-29 % compared with the control), but returned to normal level on day 30 and 90. GSH S-aryltransferase was slightly decreased on day 30 and 90, but not significant.

Table. Activity of GSH S-epoxide transferase (pmol styrene oxide/mg protein/min) and GSH S-aryltransferase (pmol CDNB/mg protein/min)

	pmol Styrene oxide/mg protein/min After		
	15	30	90
	Days		
Control CuCl	198 ± 2 141 ± 4† (-29)	165 ± 8 170 ± 10 (+3)	166 ± 5 176 ± 5 (+6)
	pmol CDNB/mg protein/min After		
	15	30	9
	Days		
Control CuCl	253 ± 2 252 ± 5 (0)	236 ± 5 219 ± 3† (-7)	255 ± 6 240 v 5 (-6)

† Statistical significance was observed at $p < 0.05$
(-) = Decrease or (+) = increase as percent of control

Reliability : (2) Reliable without restrictions
2e-Study well documented, meets generally accepted scientific principles, acceptable for assessment.

22.07.2005 (4)

5.6 GENETIC TOXICITY IN VITRO

A. BACTERIAL TEST

Type : Bacterial reverse mutation assay

Species/Strain : *Salmonella typhimurium* (strains TA 98, TA 100, TA 1535 and TA 1537) and *Escherchia coli* (strain WP2 *uvr*A)

Method : OECD TG 471 “Bacterial Reverse Mutation Test”
System of testing : Bacterial
Year : 2003
GLP : Yes
Metabolic activation : - Species and cell type: Rat (Sprague Dawley strain), male, liver
- Quantity: 5 % S9 mix induced with Aroclor 1254
Concentration tested : 3.7, 11.1, 33.3, 100, 300, and 1,000 μg/plate
Statistical Methods : Dunnett’s test
Test substance : Other TS: Copper monochloride (CuCl), purity = 97 %, Sigma-Aldrich corporation, Lot No. 17119BO
Test condition : Number of replicated: one
Frequency of Dosing: 3 plates/dose
Positive and negative control groups and treatment: Negative control - vehicle control (sterile distilled water), Positive control – 2-Nitrofluorene, Sodium azide, 9-Aminoacridine, 4-Nitroquinoline and 2-Aminoanthracene
Number of metaphases analyzed: Not analyzed
Solvent: sterile distilled water
Description of follow up repeat study: Dose range finding experiment was carried out using dose levels with 5-fold intervals of 1.6, 8, 40, 200, 1,000 and 5,000 μg/plate both in the absence and in the presence of metabolic activation system.
Criteria for evaluating results: The number of revertant colonies increased significantly in at least one strain at one or more concentrations or the data set showing a dose related correlation.
Result :
Cytotoxic conc. With metabolic activation: at above 300 μg/plate (TA 98, TA 100 and TA 1537 *E. coli* WP2 *uvr*A)
Without metabolic activation: at 1,000 μg/plate (TA 98, TA 100 and TA 1537)
Genotoxic effect Without metabolic activation: negative
With metabolic activation: negative

Table. Result of bacterial reverse mutation assay with copper monochloride

Tester strain	Chemical treated	Dose (μg/plate)	Colonies/plate (mean ± SD)	
			Without S9 mix	With S9 mix
TA 98	Test item	0	34 ± 11	23 ± 3
		3.7	26 ± 4	26 ± 7
		11.1	36 ± 7	24 ± 2
		33.3	34 ± 6	26 ± 3
		100	32 ± 7	27 ± 3
		300	27 ± 6	- [5]
		1,000	- [3]	- [5]
TA 100	Test item	0	114 ± 6	109 ± 19
		3.7	114 ± 13	122 ± 13
		11.1	128 ± 9	114 ± 15
		33.3	134 ± 17	109 ± 7
		100	132 ± 13	125 ± 15
		300	116 ± 6	- [3]
		1,000	- [3]	- [3]

TA 1535	Test item	0 3.7 11.1 33.3 100 300 1,000	14 ± 4 17 ± 2 10 ± 0 13 ± 4 12 ± 3 17 ± 3 10 ± 4	12 ± 2 13 ± 1 11 ± 7 13 ± 5 14 ± 7 13 ± 3 15 ± 10
TA 1537	Test item	0 3.7 11.1 33.3 100 300 1,000	10 ± 1 7 ± 2 8 ± 2 9 ± 3 6 ± 3 9 ± 2 - [5]	11 ± 5 12 ± 5 7 ± 3 7 ± 3 9 ± 1 - [3] - [3]
E. coli WP2 *uvr*A	Test item	0 3.7 11.1 33.3 100 300 1,000	13 ± 6 13 ± 3 12 ± 4 10 ± 1 10 ± 6 9 ± 3 6 ± 0	15 ± 3 10 ± 1 11 ± 3 10 ± 4 6 ± 1 - [3] - [3]
Positive control				
TA 98	2-NF	1.0	356 ± 23 [SS]	
	2-AA	2.0		853 ± 34 [SS]
TA 100	SA	0.5	405 ± 40 [SS]	
	2-AA	2.0		803 ± 48 [SS]
TA 1535	SA	0.5	286 ± 23 [SS]	
	2-AA	5.0		236 ± 8 [SS]
TA 1537	9-AA	50	211 ± 25 [SS]	
	2-AA	5.0		373 ± 38 [SS]
WP2 *uvr*A	4-NQ	2.0	576 ± 66 [SS]	
	2-AA	10		522 ± 15 [SS]

[3]; No colony count and thin lawn but doubt as to whether the microscopic colonies are mutants or enlarged background colonies
[5];Complete killing
[SS]; Statistical significance was observed ($p \leq 0.01$)
2-NF; 2-Nitrofluorene, 2-AA; 2-Aminoanthracene, SA; Sodium azide, 9-AA; 9-Aminoacridine, 4-NQ; 4-Nitroquinoline

Statistical result: Dunnett's test was used to compare the counts at each dose level group with the control group. High statistical significance was only observed in positive control groups.

Conclusions : No mutation in the *Salmonella typhimurium* (strains TA 98, TA 100, TA 1535 and TA 1537) and *Escherichia coli* (strain WP2 *uvr*A) occurred with copper monochloride.

Reliability : (1) Reliable without restrictions
1a - GLP guideline study

Flag : Critical study for SIDS endpoint
22.07.2005 (11)

Type : Rec assay
Species : *Bacillus subtilis*
Strain : H17 (Rec$^+$, *arg*$^-$ and *trp*-), M45 (Rec$^-$, *arg*$^-$ and *trp*$^-$)
Method : Other
System of testing : Bacteria
Year : 1980

GLP	:	No
Metabolic activation	:	Not used
Concentration tested	:	0.005 - 0.5 M
Statistical Methods	:	Not used
Test substance	:	Other TS: Copper monochloride (CuCl), Copper dichloride ($CuCl_2$), Maruichi Chemical Ltd., Misima (Japan), grade and purity were not stated`
Test conditions	:	Number of tests: not stated Positive and negative control: not stated Solvent: distilled water.
Remarks	:	*Methods:* Strains of *Bacillus subtilis* cultures were streaked rapidly from small pipettes onto B-2 agar. A 0.05 mL aliquot of each metal solution (0.005 - 0.5 M) was dropped onto a filter paper disc (diameter 10 mm) and the disk was placed on the starting point of the streak. The plates were kept at 4 °C for 24 hr and then incubated at 37 °C overnight.
Result	:	Copper monochloride and copper dichloride were negative in the rec assay.
Conclusions	:	The mutagenic activity did not occur.
Reliability	:	(3) Not reliable 3a- Documentation insufficient for assessment
22.07.2005		(6)

B. NON-BACTERIAL IN VITRO TEST

Type	:	*In vitro* Mammalian Chromosome Aberration Test
Species/Strain	:	Chinese Hamster Lung (CHL)
Method	:	OECD TG 473 “In vitro Mammalian Chromosome Aberration Test”
Year	:	2003
GLP	:	Yes
Metabolic activation	:	- Species and cell type: Rat (Sprague Dawley strain), male, liver - Quantity: S9 mix induced with Aroclor-1254
Concentration tested	:	0, 5, 10, 20, 50, 70 and 100 μg/mL
Statistical Methods	:	Fisher’s exact test
Test substance	:	Other TS: Copper monochloride (CuCl), purity = 97 %, Sigma-Aldrich corporation, Lot No. 17119BO Mitomycin C (MMC) was prepared in distilled water. Benzo(a)pyrene (BP) was prepared in anhydrous analytical grade dimethylsulfoxide (DMSO). Stock solutions of MMC and BP were stored in aliquots at –20 °C in the dark.
Test condition	:	- *Number of replicated*: one - *Frequency of Dosing*: 2 plates/dose - *Positive and negative control groups and treatment*: Negative control - vehicle control (sterile distilled water), Positive control – Mitomycin C, Benzo(a)pyrene - *Culture establishment*; CHL cells in logarithmic were to maintain low aberration frequencies. Subcultured at low density, before over growth occurs. The cells were incubated at 37 °C in atmosphere of 5 % (v/v) CO_2 and 100 % humidity. - *Number of metaphases analyzed*: 100 - *Solvent*: sterile distilled water - *Criteria for scoring aberrations*; Only cells with the modal number of chromosome 25 ± 2 were considered acceptable for analysis. Cells with greater numbers of chromosomes observed during this evaluation were noted and recorded separately. - *Description of follow up repeat study*: Series of more than three concentration levels with two-fold intervals were tested in the absence and the presence of metabolic activation system. - *Criteria for evaluating results*: The test was considered as positive in this assay if; 1) Statistically significant increase in the proportion of cells with structural aberrations (excluding gaps) occurs at one or more

concentration levels 2) 1) exceed the normal range, 3) If the result of 1) is reproducible.

Result : Significant increases in the proportion of cells with structural aberrations were observed in cultures at 50 μg/mL concentration levels both in the absence and presence of metabolic activation system. Significant increases in the proportion of cells with numerical aberrations were not observed in cultures at all concentration levels.
Since a positive result was obtained, a reproduct experiment was performed. The selected concentration levels for chromosome analysis in the absence of metabolic activation system were 50, 70, and 100 μg/mL (-S9 mix 6 + 18). In the presence of metabolic system, 20, 50, and 70 μg/mL (+S9 mix 6 + 18) were selected for concentration levels.
In the absence of metabolic system, significant increase in the proportion of cells with structural aberrations were observed in positive and negative controls at all concentration levels. Significant increases in the proportion of cells with numerical aberrations were observed in negative controls at all concentration levels.
In the presence of metabolic system, significant increase in the proportion of cells with structural aberrations were observed at 50 and 70 μg/mL concentration levels. Significant increases in the proportion of cells with numerical aberrations were observed at 70 μg/mL concentration level.

Table. Copper monochloride: Summary of structural and numerical chromosome aberrations -S9 and +S9mix, 6 hour treatment 18 hour recovery (6+18)

Treatment (μg/mL)		Replicate	Cells counted	Cells with structural aberrations (-gap)	Cells with numerical aberrations	Mitotic index (mean)
-S9 6 + 18	Distilled water	A	100	0	0	8.2
		B	100	0	0	8.6
		Total	200	0	0	8.4
	10	A	100	1	1	9.3
		B	100	1	1	9.5
		Total	200	2 NS	2 NS	9.4
	20	A	100	0	0	8.3
		B	100	1	0	8.8
		Total	200	1 NS	0 NS	8.6
	50	A	100	8	3	8.9
		B	100	8	1	9.2
		Total	200	16 SS	4 NS	9.1
	MMC 0.1 μg/mL	A	100	33	0	9.2
		B	100	24	0	9.4
		Total	200	57 SS	0 NS	9.3
+S9 6 + 18	Distilled water	A	100	0	0	8.5
		B	100	3	0	9.1
		Total	200	3	0	8.8
	10	A	100	4	1	9.2
		B	100	1	1	9.4
		Total	200	5 NS	2 NS	9.3
	20	A	100	2	0	9.5
		B	100	3	0	9.3
		Total	200	5 NS	0 NS	9.4
	50	A	100	5	0	8.9
		B	100	9	2	8.9
		Total	200	14 SS	2 NS	8.9
	B(a)P 5 μg/mL	A	100	34	1	7.8
		B	100	36	1	8.6
		Total	200	70 SS	2 NS	8.2

NS; Non statistical significance was observed

[SS]; Statistical significance was observed ($p \leq 0.05$)

Table. Copper monochloride: Summary of structural and numerical chromosome aberrations –S9 and +S9 mix, 6 hour treatment 18 hour recovery (6 + 18), confirmation experiment

Treatment (μg/mL)		Replicate	Cells counted	Cells with structural aberrations (-gap)	Cells with numerical aberrations	Mitotic index (mean)
-S9 6 + 18	Distilled water	A	100	0	0	7.5
		B	100	0	1	7.2
		Total	200	0	1	7.4
	50	A	100	5	3	7.2
		B	100	7	4	6.9
		Total	200	12 [SS]	7 [SS]	7.1
	70	A	100	12	10	2.5
		B	100	10	8	3.1
		Total	200	22 [SS]	18 [SS]	2.8
	100	A	100	16	11	4.4
		B	100	20	9	2.5
		Total	200	36 [SS]	20 [SS]	3.5
	MMC 0.1 μg/mL	A	100	17	0	7.5
		B	100	19	0	7.7
		Total	200	36 [SS]	0 [NS]	7.6
+S9 6 + 18	Distilled water	A	100	1	0	9.1
		B	100	1	1	9.0
		Total	200	2	1	9.1
	20	A	100	4	3	8.9
		B	100	2	0	9.2
		Total	200	6 [NS]	3 [NS]	9.1
	50	A	100	5	1	9.5
		B	100	9	2	8.9
		Total	200	14 [SS]	3 [NS]	9.2
	70	A	100	12	3	7.4
		B	100	23	7	4.5
		Total	200	35 [SS]	10 [SS]	6.0
	B(a)P 5 μg/mL	A	100	33	1	7.1
		B	100	31	1	6.8
		Total	200	64 [SS]	2 [NS]	7.0

[NS]; Non statistical significance was observed
[SS]; Statistical significance was observed ($p \leq 0.05$)

Conclusions : Copper monochloride exhibited clastogenic activity in cultured Chinese Hamster Lung cells when tested under the conditions employed for this test.
Reliability : (1) Reliable without restriction
1a - GLP guideline study
Flag : Critical study for SIDS endpoint
22.07.2005 (14)

5.7 GENETIC TOXICITY IN VIVO

Type : Mammalian erythrocyte micronucleus test
Species/Strains : Mouse/ICR (SPF)
Sex : Male
Method : OECD TG 474 “Genetic Toxicity: Micronucleus Test”
Year : 2003
GLP : Yes
Route of administration : Negative control-oral injection, positive control-Intraperitoneal injection

Dose : Three dose levels, 15, 30 and 60 mg/kg bw/day, were determined for the micronucleus experiment based on the results of dose range finding experiment.
Exposure period : 24 hours
Statistical methods : Chi-square test (using a 2 × 2 contingency table)
Test substance : Other TS: Copper monochloride (CuCl), purity = 99 %, Sigma-Aldrich corporation, LOT No. 17119BO
Test condition : - Age at study initiation: 8 weeks
- No. of animals per dose: 6
- Vehicle: 0.5 % Carboxy methylcellulose (CMC) (LOT No.-32K0007)
- Frequency of treatment: duplicate treatments (only positive control group was dosed once)
- Sampling times: 24 hours after administration
- Control groups and treatment: Negative control (0.5 % CMC), Positive control (2.0 mg/kg of Mitomycin C)
- Clinical observations performed: Yes
- Organs examined at necropsy: not examined
- Criteria for evaluating results: at least 1,000 polychromatic erythrocytes per animals were scored for the incidence of micronuclei.
Result : *Main test:*
All animals dosed with copper monochloride exhibited similar PCE/(PCE + NCE) ratios and MNPCE frequencies compare to those of negative control animals. All frequencies of MNPCE in the negative control groups fell within acceptable ranges, while the positive control groups induced clear increase in the frequencies of MNPCE.

Table. Summary of PCE/(PCE+NCE) ratio and MNPCE frequency

Treatment group	Dose (mg/kg)	PCE/(PCE + NCE) (mean ± S.D.)	MNPCE per 1,000 PCE (mean ± S.D.)
Vehicle	0	0.500 ± 0.004	0.9 ± 0.5
Copper monochloride	15	0.500 ± 0.005	0.8 ± 0.4
	30	0.497 ± 0.011	0.9 ± 0.6
	60	0.500 ± 0.008	0.8 ± 0.4
Mitomycin C	2	0.495 ± 0.003	84.5* ± 5.2

*: Indicate significant difference at $p \leq < 0.01$ level
MNPCE; Micronucleated polychromatic erythrocyte, PCE; Polychromatic erythrocyte, NCE; Normochromatic erythrocyte

Genotoxic effects : Negative
Conclusion : It is concluded that copper monochloride did not induce micronuclei in the mice bone marrow cells under the conditions employed for this test.
Reliability : (1) Reliable without restriction
1a - GLP guideline study
Flag : Critical study for SIDS endpoint
22.07.2005 (15)

5.8 CARCINOGENICITY

5.9 REPRODUCTIVE TOXICITY

A. TOXICITY TO REPRODUCTION

Species/strains : Rat / Sprague-Dawley
Sex : Male / Female
Method : OECD TG 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year : 2004

GLP : Yes
Route of administration : Oral (Gavage)

Dose levels : 0, 1.3, 5, 20 and 80 mg/kg bw/day
Exposure period : 30 days for males and 39 to 51 days for females
Frequency of treatments : Daily
Control groups : Yes (Concurrent no treatment)
Premating exposure period : 2 weeks
Statistical methods : This is the same as describe above the first study of section 5.4 repeated dose toxicity
Test substance : Other TS: Copper monochloride, purity = 97 %, Sigma-Aldrich Corporation, LOT No. – 17119BO
Test conditions : **Test organism**
- Sex: male/female
- Age at study initiation: 7 week-old animals
- Body weights at study initiation: 297.0 - 369.6 g for males and 180.3 - 222.3 g for females
- No. of animals per sex per dose: 12

Observation of F0
- *Mating*: The day verified by sperm in a vaginal rinse was designated as day 0 of pregnancy. Based on these results, the following index was calculated.
Copulation index = (No. of animals with successful copulation / No. of mated animals) × 100
Fertility index (male) = (No. of impregnating animals / No. of animals with successful copulation) × 100
Pregnancy index (female) = (No. of pregnant animals / No. of animals with successful copulation) × 100
- *Sperm examination*: During the necropsy of the males, testis and epididymis of 5 animals selected from each group were removed and then weighed. Also sperm head counts, motility, and sperm morphology were examined.
- *Hormone measurement*: Ten males were selected from each test group at necropsy. Blood was collected from abdominal artery and centrifuged to obtain serum.
- *Gross findings*: All adult animals were subject to a detailed gross necropsy, which includes careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities including their contents. The following organs were weighed: testis, epididymis, prostate, seminal vesicle or ovaries and uterus.
- *Histopathological examination*: Following organs of the selected animals in the high dose groups and the controls were preserved in 10 % buffered formalin solution: ovary, uterus, vagina, seminal vesicle, and mammary gland. The testis and epididymis were preserved in Bouin fixative.

NOAELs : 80 mg/kg bw/day for both sexes
Results : **Results for F0**
- *Precoital time, fertility and mating data*: There were no statistically significant differences compared with the controls. The results in detail were shown in table.
- *Sperm examination*: No statistical significances were observed except that the number of sperms in cauda epididymis was statistically increased in the 1.3 and 5 mg/kg bw/day groups, but it was not dose-dependent findings.
- *Hormone measurement*: There were no statistically significant differences in the serum testosterone levels of all male treatment groups.
- *Gross findings*: Each case of paleness of testies, epididymis, prostate gland and seminal vesicle was found in the 80 mg/kg bw/day male group. There were no abnormal findings in all female groups.

- *Organ weights*: For male rats, absolute organ weight of seminal vesicle was decreased in the 20 mg/kg bw/day groups. No abnormal findings were observed in other genital organs of each sex
- *Histopathological findings*: There were no chemical-related findings in all treatment groups.

Table. Precoital time and fertility data of parent animals

Dose (mg/kg bw/day)	0	1.3	5	20	80
No. of females paired	12	12	12	12	12
No. of females mated	12	12	12	12	10
Precoital time (days) (mean ± SD)	3.5 ± 3.26	2.5 ± 1.31	2.0 ± 1.04	1.6 ± 0.90	2.6 ± 1.26
Male					
No. of mated animals	12	12	12	12	10
Copulation index (%)	12/12 (100)	12/12 (100)	12/12 (100)	12/12 (100)	10/10 (100)
Fertility index (%)	12/12 (100)	12/12 (100)	11/12 (91.7)	12/12 (100)	9/10 (90)
Female					
No. of mated animals	12	12	12	12	10
Copulation index (%)	12/12 (100)	12/12 (100)	12/12 (100)	12/12 (100)	10/10 (100)
Pregnancy index (%)	12/12 (100)	12/12 (100)	11/12 (91.7)	12/12 (100)	9/10 (90)

Conclusions : No treatment changes were observed in precoital time, mating index, fertility index, pregnancy index, sperm toxicity parameters and serum testosterone. NOAEL of reproductive toxicity was 80 mg/kg bw/day of parent animals.
Reliability : (1) Reliable without restrictions
1a - GLP guideline study (OECD)
Flag : Critical study for SIDS endpoint
22.07.2005 (12)

B. DEVELOPMENTAL TOXICITY / TERATOGENICITY

Species/strains : Rat / Sprague-Dawley
Sex : Male / Female
Route of administration : Oral (Gavage)
Method : OECD TG 422 “Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test”
Year : 2004
GLP : Yes
Dose levels : 0, 1.3, 5, 20 and 80 mg/kg bw/day
Exposure period : 30 days for males and 39 to 51 days for females
Frequency of treatment : Daily
Control groups : Yes (Concurrent no treatment)
Statistical methods : This is the same as describe above the first study of section 5.4 repeated dose toxicity
Test substance : Other TS: Copper monochloride, purity = 97 %, Sigma-Aldrich Corporation, LOT No. 17119BO
NOAEL : 20 mg/kg bw/day

Test conditions : **Test organism of F0**
- Sex: male/female
- Age at study initiation: 7 week-old animals
- Body weights at study initiation: 297.0 - 369.6 g for males and 180.3 - 222.3 g for females
- No. of animals per sex per dose: 12

Observation of F0
- Observation of pregnancy and delivery
- Preganacy period
- No. of implantation and corpus lutea
- Delivery index = (No. of dams with live newborns / No. of pregnant dams) × 100

Observation of F1
- No. of perinatal death
- No. of live young on day 0 and 4 at postpartum
- No. of pups with gross lesions
- No. of pups with runts
- Viability index at day 4 of postpartum = (No. of live pups at day 4 / No. of live pups at birth) × 100
- Body weights of pups on day 0 and 4 at postpartum

Results : **Results for F0 and F1**
- No statistically significant differences were seen in the following parameters examined: pregnancy period, number of implantations, viability index, sex ratio and body weights of newborns.
- The number of corpus lutea was statistically decreased in the 1.3 and 5 mg/kg bw/day groups, when compared with the controls. Three pups showed a gross lesion, namely icterus in the 80 mg/kg bw/day group. The incidence of runts was statistically increased in the 80 mg/kg bw/day. There were no pups with gross lesions in all treatment groups on day 4 of postpartum.

Table. Reproductive and littering findings of dams (sex: female)

Dose (mg/kg bw/day)	0	1.3	5	20	80
No. of dam	12	12	11	12	9
Gestation length (day) (Mean ± S.D.)	21.5 ± 0.33	21.5 ± 0.43	21.6 ± 0.32	21.6 ± 0.42	21.8 ± 0.26
No. of corpora lutea (Mean ± S.D.)	18.3 ± 4.66	15.7 ± 2.15‡	15.2 ± 2.40‡	15.7 ± 2.23	16.8 ± 2.49
No. of implantations (Mean ± S.D.)	14.8 ± 1.90	14.1±1.68	13.8 ± 1.99	14.6 ± 1.56	14.1 ± 1.05
No. of perinatal deaths	0	0	0	0	3
No. of live young at birth Male Female Total	 86 84 170	 81 85 166	 71 71 142	 89 76 165	 63 57 120
No. of live young at day 4 Total	 167	 165	 139	 163	 120
No. of pups with gross lesions (%) 0 day 4 day	 0 0	 0 0	 0 0	 0 0	 3 (2.5) ‡a 0
No. of pups with runts (%)	0	0	0	0	4 (3.2) ‡
Viability index (Mean ± S.D.)	98.4 ± 3.93	99.4 ± 2.22	98.1 ± 3.27	98.8 ± 4.12	100 ± 0
Delivery index	100	100	100	100	100
Body weights of pups Male 0 day (g)	 6.6 ± 0.47	 6.6 ± 0.49	 6.9 ± 0.49	 6.7 ± 0.44	 6.3 ± 0.49

(Mean ± S.D.) Male 4 day (g) (Mean ± S.D.)	10.4 ± 0.88	10.3 ± 0.84	11.0 ± 1.09	10.4 ± 0.96	10.0 ± 9.40
Female 0 day (g) (Mean ± S.D.)	6.2 ± 0.39	6.2 ± 0.43	6.6 ± 0.47	6.3 ± 0.36	6.0 ± 0.48
Female 4 day (g) (Mean ± S.D.)	10.1 ± 0.94	9.7 ± 0.95	10.5 ± 0.95	10.0 ± 0.97	9.7 ± 0.96

‡: Statistical significance was observed at $p < 0.05$
[a] : Icterus

Table. The effects in pups according to dams in the 80 mg/kg bw/day group.

No. of dam	Occurrence of effects
110	One icterus, two runts (one male and one female)
117	One icterus
120	One icterus, two runts (one male and one female)

Conclusions : There were no treatment-related changes in all parameters of offsprings during the parturition and lactation periods except that icterus and runts were observed in a few offsprings on day 1 postpartum in the 80 mg/kg bw/day groups.
Reliability : (1) Reliable without restrictions
1a-GLP guideline study (OECD)
Flag : Critical study for SIDS endpoint
22.07.2005 (12)

5.10 OTHER RELEVANT INFORMATION

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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