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October 15, 1992

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Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91 CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
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3/14/95

ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation's TSCA §8(e) reporting standard². This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.³ Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

²In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment. See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

³A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteria. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent⁴, the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- o the "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.⁵
- o the "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- o the "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.

⁴The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

⁵ See, e.g., 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). See also, Rollins Environmental Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

"a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, *See*, 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy", 43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide*.

<u>TEST TYPE</u>	<u>1978 POLICY CRITERIA EXIST?</u>	<u>New 1991 GUIDE CRITERIA EXIST?</u>
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	} ⁶	} ⁷
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y ⁸
SKIN SENSITIZATION (ANIMALS)	N	Y ⁹
EYE IRRITATION	N	Y ¹⁰
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y ¹¹
REPRODUCTION STUDY	N	Y ¹²
DEVELOPMENTAL TOX	Y ¹³	Y ¹⁴

⁶43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporting of specific effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemical. unknown effects occurring during such a range test may have to be reported if they are those of concern to the Agency and if the information meets the criteria set forth in Parts V and VII."

⁷Guide at pp.22, 29-31.

⁸Guide at pp-34-36.

⁹Guide at pp-34-36.

¹⁰Guide at pp-34-36.

¹¹Guide at pp-22; 36-37.

¹²Guide at pp-22

¹³43 Fed Reg at 11112

"Birth Defects" listed.

¹⁴Guide at pp-22

NEUROTOXICITY	N	Y ¹⁵
CARCINOGENICITY	Y ¹⁶	Y ¹⁷
MUTAGENICITY		
<i>In Vitro</i>	Y ¹⁸	Y ¹⁹
<i>In Vivo</i>	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y} ²⁰	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reproductive	N	N

¹⁵Guide at pp-23; 33-34.

¹⁶43 Fed Reg at 11112
"Cancer" listed

¹⁷Guide at pp-21.

¹⁸43 Fed Reg at 11112; 11115 at Comment 15

"Mutagenicity" listed/ *in vivo* vs *in vitro* discussed; discussion of "Ames test".

¹⁹Guide at pp-23.

²⁰43 Fed Reg at 11112; 11115 at Comment 16.

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Report No. 24-54

August 27, 1954

MR-118-073

TOXICITY OF UREA HERBICIDES, INTERMEDIATES, AND CATALYSTS

Medical Research Projects Nos. MR-18, MR-221, and MR-263

HASKELL LABORATORY FOR TOXICOLOGY
AND INDUSTRIAL MEDICINE

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TOXICITY OF UREA HERBICIDES, INTERMEDIATES, AND CATALYSTS

Medical Research Projects Nos. MR-48, MR-221, and MR-263

For the past four years, work has been in progress at the Haskell Laboratory to evaluate the toxicity of various urea herbicides as well as intermediate compounds and catalysts involved in their synthesis. The requested determinations have been completed using the following compounds:

3-(p-chlorophenyl)-1,1-dimethylurea
3-(o-chlorophenyl)-1,1-dimethylurea
3-(m-chlorophenyl)-1,1-dimethylurea
tetramethylurea
p-chlorophenylurea
p-chloroaniline
1,1-dimethyl-3-phenylurea
3-(p-methoxyphenyl)-1,1-dimethylurea
3-(3,4-dichlorophenyl)-1,1-dimethylurea
3,4-dichlorophenylurea
3,4-dichloroaniline
1-(3,4-dichlorophenyl)-1,3,3-trimethylurea
1-(3,4-dichlorophenyl)-3-methylurea
3-(3,4-dichlorophenyl)-1,1-diethylurea
3-(3,4-dichlorophenyl)-1-methyl-1-ispropylurea
3-(3,4-dichlorophenyl)-1-methyl-1-sec-butylurea

The results of these experiments are given in detail in the following text. A summary in tabular form for convenient reference is to be found at the end of the report.

3-(p-CHLOROPHENYL)-1,1-DIMETHYLUREA

Investigation of the toxicity of 3-(p-chlorophenyl)-1,1-dimethylurea has been carried out. The tests employed to determine the nature of the toxicity when the material is taken orally were as follows:

1. The Approximate Lethal Dose (ALD) was determined for rats, guinea pigs, and rabbits.
2. The LD₅₀, or dose that would kill 50 per cent of the animals, was determined for rats.
3. The cumulative toxicity caused by repeated administration of sublethal doses (one-fifth ALD) to rats was studied.
4. The effect of adding 3-(p-chlorophenyl)-1,1-dimethylurea to the daily diet of rats was studied for a six-week period.

CAS# 587-34-8; 582-44-5; 140-38-5; 632-22-4;
106-47-8; 95-76-1

CHEM: 3-(o-chlorophenyl)-1,1-dimethylurea;
3-(m-chlorophenyl)-1,1-dimethylurea;
tetramethylurea; p-chlorophenylurea;
p-chloroaniline; 1,1-dimethyl-3-phenylurea;
3-(p-methoxyphenyl)-1,1-dimethylurea;
3,4-dichlorophenylurea; 3,4-dichloroaniline;
1-(3,4-dichlorophenyl)-1,3,3-trimethylurea
1-(3,4-dichlorophenyl)-3-methylurea
3-(3,4-dichlorophenyl)1,1-diethylurea;
3-(3,4-dichlorophenyl)-1-methyl-1-isopropylurea;
3-(3,4-dichlorophenyl)-1-methyl-1-sec-butylurea

TITLE: Toxicity of Urea Herbicides, Intermediates
and Catalysts

DATE: 8/27/54

SUMMARY OF EFFECTS:

ORAL ALD/subacute 3-(o-chlorophenyl)-1,1-dimethylurea - incoordination

ORAL ALD/subacute 3-(m-chlorophenyl)-1,1-dimethylurea - incoordination
tetramethylurea - nothing to report

ORAL ALD/subacute p-chlorophenylurea - incoordination/weakness in
hindquarters

ORAL ALD/subacute p-chloroaniline - incoordination

ORAL ALD/LD50 1,1-dimethyl-3-phenylurea - weakness in hindquarters

ORAL ALD/subacute 3-(p-methoxyphenyl)-1,1-dimethylurea -
incoordination/paralysis

ORAL ALD/subacute 3,4-dichlorophenylurea - incoordination

ORAL ALD/subacute 3,4-dichloroaniline - cyanosis/methemoglobinemia

1-(3,4-dichlorophenyl)-1,3,3-trimethylurea - nothing to report

Subacute 1-(3,4-dichlorophenyl)-3-methylurea - incoordination/blood
destruction

ALD subacute 3-(3,4-dichlorophenyl)1,1-diethylurea - blood
destruction/cyanosis

3-(3,4-dichlorophenyl)-1-methyl-1-isopropylurea - nothing to report;

3-(3,4-dichlorophenyl)-1-methyl-1-sec-butylurea - nothing to report

In addition to the oral studies, other phases of the toxicity of 3-(p-chlorophenyl)-1,1-dimethylurea were investigated. The effects of absorption of this compound through the skin were studied using the rabbit. Skin irritation and sensitization tests were carried out on guinea pigs. The urine of rats and dogs which had been fed 3-(p-chlorophenyl)-1,1-dimethylurea was also analyzed to determine the metabolic products. The effects of chronic oral exposure of dogs to this chemical will be reported at a later date, after the experiment has been completed.

For these investigations two samples of 3-(p-chlorophenyl)-1,1-dimethylurea were used. The first, coded IN 12,402, TD 1026-4A (Haskell No. 479) was used to determine the ALD for rats as well as the skin irritation and sensitization on guinea pigs. For all other determinations sample 1332-35 (Haskell No. 579) was used.

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 7500 mg/kg of body weight for male albino rats when the 3-(p-chlorophenyl)-1,1-dimethylurea was administered by stomach tube as a 10 or 30 per cent suspension in peanut oil containing 20 per cent acetone. The animals receiving sublethal doses were weak, pale, cyanotic, and frequently paralyzed in the hind legs. The higher doses caused labored respiration, marked weakness, and unconsciousness. When the survivors were sacrificed ten days after treatment, autopsy revealed enlarged, dark, and congested spleens containing foci of blood formation. These findings suggest red blood cell destruction and compensatory erythropoiesis.

The ALD of 3-(p-chlorophenyl)-1,1-dimethylurea for guinea pigs receiving a 30 per cent suspension by stomach tube was found to be 670 mg/kg of body weight. The animals receiving sublethal doses showed marked weakness and loss of weight. When they were sacrificed ten to twelve days after treatment, there was no significant pathology, although one animal showed evidence of healed kidney injury. The guinea pigs receiving lethal doses showed weakness and paralysis with slow respiration and lacrimation. The animals which had received sublethal doses showed no significant pathology.

The ALD of 3-(p-chlorophenyl)-1,1-dimethylurea for rabbits receiving a 20 per cent suspension in peanut oil was found to be 1500 mg/kg of body weight. The animals receiving 200 and 450 mg/kg showed no clinical signs and no pathology when they were sacrificed twelve days after treatment. The rabbits which received 670 and 1000 mg/kg showed a loss of appetite and weakness. When they were sacrificed ten days after treatment, no significant pathology was found. The animals receiving lethal doses became unconscious soon after treatment and died within twenty hours. Advanced post mortem change obscured any pathology which may have been present.

More precise than the ALD as an estimate of acute toxicity is the LD₅₀. For this determination, a series of dose levels, spaced at equal logarithmic intervals, was chosen. Five groups of ten male albino rats each received 3-(p-chlorophenyl)-1,1-dimethylurea in peanut oil at the calculated dose levels. The LD₅₀, or dose that kills 50 per cent of the animals, was calculated to be 3600 mg/kg of body weight, with confidence limits of 2900 to 4400 mg/kg. All of the rats which died suffered from pulmonary edema and congestion which was frequently accompanied by anemia of the liver, kidneys, and spleen. All of the survivors showed symptoms of methemoglobinemia, such as cyanosis, enlarged, dark spleen, and compensatory red blood cell formation in the spleen and bone marrow. A few animals showed kidney pathology which may also have been due to the test chemical.

Subacute Oral Toxicity

Doses of 1500 mg/kg of body weight (one-fifth ALD) were administered by stomach tube to each of six male albino rats five times a week. By the eighth treatment, all six animals had died. During the treatments the animals showed discomfort and weakness and lost weight continuously. Autopsy revealed pulmonary edema and congestion as well as damage to the liver, kidneys, and spleen.

Because the LD₅₀ was much lower than the ALD and because the repeated doses of 1500 mg/kg had produced such severe cumulative toxicity, the subacute dose was reduced to 500 mg/kg administered five times a week for two weeks. The animals showed discomfort after treatments, lost weight continuously, and became cyanotic. During the observation period they regained weight almost to the original level. All of the animals were sacrificed ten days after the final treatment. At autopsy the spleens were large, dark, and congested, with small foci of blood formation in all cases. The deposition of brown granules of blood pigment (hemosiderin) in the spleen was indicative of blood destruction.

Subacute Oral Toxicity - Feeding Experiment

Three groups of weanling rats, each consisting of five males and five females, were fed a known amount of 3-(p-chlorophenyl)-1,1-dimethylurea in ground chow, and their food consumption was compared with that of a control group of male and female rats. The three test groups received 0.005, 0.05, and 0.5 per cent 3-(p-chlorophenyl)-1,1-dimethylurea, respectively. Blood counts for all rats were done at the end of one month. The experiment terminated at the end of the sixth week.

The rats receiving 0.005 per cent 3-(p-chlorophenyl)-1,1-dimethylurea were comparable to the controls in food consumption and weight gain. Blood counts were within the normal range and no clinical signs were observed. When the animals were sacrificed after the sixth week, two of the five males showed evidence of methemoglobinemia and/or compensatory red blood cell formation. None of the females showed any significant pathology.

Both the male and female rats receiving 0.05 per cent 3-(p-chlorophenyl)-1,1-dimethylurea were comparable to the controls in food consumption and weight gain. They showed no clinical signs and blood counts were within the normal range. When the rats were sacrificed at the end of the experiment, signs of methemoglobinemia were again apparent and compensatory red blood cell formation was found in the spleen and occasionally the bone marrow.

The rats receiving 0.5 per cent 3-(p-chlorophenyl)-1,1-dimethylurea consumed much less food and gained considerably less weight than the control group. The rats were pale and cyanotic. Their blood count was lower than that of the control rats. Many degenerated cells were present and the blood itself was dark brown. When the animals were sacrificed at the end of the sixth week, autopsy revealed that there was methemoglobinemia as well as possible blood destruction. Compensatory red blood cell formation was found in the spleen and bone marrow of all animals.

When this feeding experiment is considered as a whole, it is evident that the diets containing 0.005 and 0.05 per cent 3-(p-chlorophenyl)-1,1-dimethylurea have little or no effect on the food consumption or growth of rats, whereas 0.5 per cent 3-(p-chlorophenyl)-1,1-dimethylurea in the diet inhibits both. The comparative hematology is shown in Table I. While the red cell count remained within the normal range for rats of this strain, there was a decrease in this count which ran parallel to the increase in the amount of 3-(p-chlorophenyl)-1,1-dimethylurea in the diet. The hemoglobin content of the blood was slightly lower at the 0.005 and 0.05 per cent dose levels and was still lower at the 0.5 per cent level. There were only two cases of methemoglobinemia and/or blood destruction at the lowest dose level. All of the animals receiving 0.05 and 0.5 per cent 3-(p-chlorophenyl)-1,1-dimethylurea in the diet showed evidence of methemoglobinemia and compensatory erythropoiesis.

Acute Skin Absorption Toxicity

A 20 per cent suspension of 3-(p-chlorophenyl)-1,1-dimethylurea in dimethyl phthalate was applied to the shaven skin between the shoulders of a male rabbit. A dose of 2250 mg/kg, the maximum feasible dose, was rubbed into the skin with a glass rod over an eight-hour period. Five hours after treatment, the material was caked on the back of the animal. Within two days the material had disappeared and the rabbit showed no clinical signs. When the animal was sacrificed eleven days after treatment, no significant pathology was found.

Primary Irritation and Sensitization of the Skin

A 33 per cent water paste of 3-(p-chlorophenyl)-1,1-dimethylurea was applied to the intact and abraded skin of male albino guinea pigs. The compound was practically non-irritating and did not cause allergic skin sensitization.

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TABLE I

BLOOD COUNTS

	RBC	WBC	Hbg	Differential				
				P	L	M	E	NR
Control Group "A"								
Male	7,110,000	15,800	13.2	11.4	86.4	0.4	2.2	0.0
Female	7,050,000	18,020	12.9	11.2	86.8	0.4	1.6	0.0
Group "B" 0.5% 3-(p-chlorophenyl)-1,1-dimethylurea								
Male	6,372,000	22,780	11.8	9.4	89.0	0.0	1.6	6.0
Female	6,372,000	20,040	12.1	11.8	86.4	0.0	1.8	4.2
Group "C" 0.05% 3-(p-chlorophenyl)-1,1-dimethylurea								
Male	6,840,000	19,960	12.5	10.4	87.0	0.8	1.8	0.6
Female	6,870,000	17,120	12.0	10.8	86.2	0.4	2.6	0.2
Group "D" 0.005% 3-(p-chlorophenyl)-1,1-dimethylurea								
Male	7,020,000	21,800	12.5	10.6	88.6	0.0	0.8	0.0
Female	6,840,000	17,160	12.7	8.8	89.6	0.6	1.0	0.0

Key: RBC - red blood cells
 WBC - white blood cells
 Hbg - hemoglobin
 P - polymorphonuclear leucocytes
 L - lymphocytes
 M - monocytes
 E - eosinophils
 NR - nucleated red cells

Products of the Metabolism of 3-(p-Chlorophenyl)-1,1-dimethylurea

Traces of p-chloroaniline were isolated from the urine of men working with 3-(p-chlorophenyl)-1,1-dimethylurea. The maximum found was 12 micrograms/50 ml urine and there was some question as to the origin of the compound: Did it occur as a contaminant of 3-(p-chlorophenyl)-1,1-dimethylurea, or did it result from metabolic breakdown? Chemical analysis of a supposedly pure sample of 3-(p-chlorophenyl)-1,1-dimethylurea failed to reveal the presence of p-chloroaniline.

In order to determine the metabolic products of 3-(p-chlorophenyl)-1,1-dimethylurea, a 20 per cent suspension of the pure material was administered orally to each of three rats. For the first four treatments, each animal received 1000 mg/kg of body weight. Because the rats were then in poor condition, the dose was reduced to 500 mg/kg for the last two treatments. Urine specimens were collected, pooled, and extracted with ether. The ether-extracted material gave a negative test for free p-chloroaniline. After hydrolysis with sulfuric acid, however, the test for p-chloroaniline was positive. Its presence was confirmed by its melting point and by the preparation of its acetamide derivative. Therefore, the ether-extracted material was a conjugate of p-chloroaniline, possibly the ethereal sulfate. Analyses of the urine of dogs fed 3-(p-chlorophenyl)-1,1-dimethylurea gave similar results.

Summary and Conclusions

The acute oral toxicity of 3-(p-chlorophenyl)-1,1-dimethylurea was found to vary considerably with species. For rats, the ALD was 7500 mg/kg of body weight, but the LD₅₀ was only 3600 mg/kg with confidence limits of 2900 to 4400 mg/kg. The ALD for rabbits was 1500 mg/kg, while the value for guinea pigs was 670 mg/kg. Slow respiration, lacrimation, and weakness were characteristic clinical signs in all three species. In addition, the rats were cyanotic and frequently paralyzed in the hind legs. The pathology found when the rabbits and guinea pigs were autopsied was not well defined. The rats, on the other hand, showed a definite pathological pattern: The animals which died suffered from pulmonary edema and congestion, which was frequently accompanied by anemia of the liver, kidneys, and spleen; the survivors showed evidence of methemoglobinemia with compensatory red blood cell formation in the spleen and bone marrow.

Repeated doses of 1500 mg/kg produced such severe cumulative toxicity that all the animals had died by the end of the eighth treatment. Pulmonary edema and congestion as well as possible injury to the liver and kidneys were apparent at autopsy. When the subacute doses were reduced to 500 mg/kg, all the animals survived. After they were sacrificed, autopsy revealed enlarged, darkened, and congested spleens with foci of blood formation present, which would imply methemoglobinemia with compensatory red blood cell formation.

Both male and female rats which were fed 0.5 per cent 3-(p-chlorophenyl)-1,1-dimethylurea in their diet consumed less food and gained less weight than the control groups. They suffered from methemoglobinemia, which

was compensated for by increased red blood cell formation in the spleen and bone marrow. The rats receiving 0.05 per cent 3-(p-chlorophenyl)-1,1-dimethylurea showed no clinical signs, but autopsy showed evidence of methemoglobin formation with compensatory erythropoiesis. Of the five males receiving 0.005 per cent 3-(p-chlorophenyl)-1,1-dimethylurea, two showed evidence of methemoglobinemia and/or erythropoiesis. The females in this group showed no pathology. Comparative hematology revealed that there was a gradual decrease in the red cell count with the increasing concentration of 3-(p-chlorophenyl)-1,1-dimethylurea in the diet. The hemoglobin content was slightly lower than the control level for all three groups, 0.005 and 0.05 per cent being similar and 0.5 per cent being the lowest.

A 30 per cent water paste of 3-(p-chlorophenyl)-1,1-dimethylurea was found to be practically non-irritating to the intact and broken skin of guinea pigs. It did not produce allergic skin sensitization.

A dose of 2250 mg/kg was applied to the skin of a rabbit to determine the absorption toxicity of 3-(p-chlorophenyl)-1,1-dimethylurea. The animal showed no clinical signs and no significant pathology.

Chemical analyses of the urine of rats and dogs fed 3-(p-chlorophenyl)-1,1-dimethylurea showed that the metabolic product of 3-(p-chlorophenyl)-1,1-dimethylurea was a conjugate of p-chloroaniline.

From the data obtained from these experiments, it would appear that a moderate amount of skin contact with 3-(p-chlorophenyl)-1,1-dimethylurea would not be harmful because it is not an irritant or a sensitizer, nor is it significantly absorbed through the skin. On the other hand, the compound may enter the body by other routes to produce cumulative toxicity. It is therefore necessary that due care be exercised in the general handling of 3-(p-chlorophenyl)-1,1-dimethylurea.

ISOMERS OF 3-(p-CHLOROPHENYL)-1,1-DIMETHYLUREA

The ortho and meta isomers, 3-(o-chlorophenyl)-1,1-dimethylurea and 3-(m-chlorophenyl)-1,1-dimethylurea, were also tested for toxicity to determine how these compounds would compare with the para compound. The acute and subacute oral toxicity as well as skin irritation and sensitization properties were determined for both compounds. The sample of ortho compound was coded NB 2390-14 (Haskell No. 743); the meta isomer was NB 2390-20 (Haskell No. 744).

3-(o-Chlorophenyl)-1,1-dimethylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) of 3-(o-chlorophenyl)-1,1-dimethylurea was found to be 3400 mg/kg of body weight for male albino rats when the material was administered by stomach tube as a 30 per cent suspension

in peanut oil. All the animals receiving 1000 mg/kg or more were pale and frequently cyanotic. Labored respiration and incoordination were also characteristic. Rats receiving lethal doses lapsed into a coma and died within twenty hours with pulmonary edema and congestion. Animals receiving sublethal doses lost weight for several days after treatment. When they were sacrificed ten days after treatment, autopsy revealed that the animal receiving 1500 mg/kg suffered liver injury. The others showed no significant pathology.

Subacute Oral Toxicity

Doses of 680 mg/kg (one-fifth ALD) were administered orally to each of six male albino rats five times a week for two weeks. Two animals died after the third treatment, three after the fourth, and the last one after the ninth. Autopsy revealed pulmonary edema and congestion, gastric ulceration and atony, and hepatitis.

In view of these results, this test was repeated, using doses of 400 mg/kg. The symptoms of this group were the same as the first, and two of the six rats died of pulmonary edema and congestion, hepatitis, and gastritis. The animals which survived were sacrificed ten days after the final treatment. Autopsy showed consistent hepatitis.

When the subacute dose was reduced to 300 mg/kg for another group of rats, all six survived. The animals were frequently pale, cyanotic, restless, and incoordinated during the course of the treatments. They were sacrificed and autopsied ten days after the final treatment. Four of the six rats showed evidence of hepatitis. The weight of the kidneys as well as the liver was higher than the normal average, indicating the possibility of kidney damage in addition to the hepatitis.

Primary Irritation and Sensitization of the Skin

3-(o-Chlorophenyl)-1,1-dimethylurea was found to be non-irritating to the intact skin of guinea pigs when the material was applied as a 33 or 50 per cent water paste. On abraded skin, a 15 per cent water paste was mildly irritating and a 33 per cent water paste was moderately irritating. The compound did not produce allergic skin sensitization in guinea pigs.

Summary

The ALD for 3-(o-chlorophenyl)-1,1-dimethylurea was found to be 3400 mg/kg when the material was administered orally to rats. The animals were pale, cyanotic, and incoordinated. Lethal doses caused prompt death due to pulmonary edema and congestion. One sublethal dose produced hepatitis.

3-(o-Chlorophenyl)-1,1-dimethylurea was found to produce severe cumulative toxicity. Repeated doses of 680 mg/kg caused death due to pulmonary edema and congestion in all six cases. Repeated doses of 400 mg/kg killed two of six rats, and produced hepatitis in the four survivors. When the dose was reduced to 300 mg/kg, all six animals survived. Four of these showed evidence of hepatitis.

A 33 or 50 per cent water paste of 3-(o-chlorophenyl)-1,1-dimethylurea was non-irritating to the intact skin of guinea pigs. On abraded skin, the 33 per cent paste was moderately irritating, while a 15 per cent paste was mildly irritating. No allergic skin sensitization was produced.

3-(m-Chlorophenyl)-1,1-dimethylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) of 3-(m-chlorophenyl)-1,1-dimethylurea was found to be 7500 mg/kg of body weight for male albino rats when the material was administered by stomach tube as a 30 per cent suspension in peanut oil. All the animals were weak, pale, and cyanotic. The rats which received sublethal doses were sacrificed twelve days after treatment. Autopsy revealed large, dark, and congested spleens with foci of blood formation, but no abnormal deposition of blood pigment. There is, therefore, no evidence of blood destruction. However, the foci of blood formation in the spleen may be a compensatory mechanism to replace red cells in which the hemoglobin is modified by the 3-(m-chlorophenyl)-1,1-dimethylurea so that it cannot carry oxygen. The animals receiving the lethal dose died within twenty hours. The pathology suggested that the liver and kidneys were affected.

Subacute Oral Toxicity

Doses of 500 mg/kg were administered orally to each of six male albino rats five times a week for two weeks. All of the animals showed discomfort, incoordination, and weight loss. One rat became pale, cyanotic, and weak after the tenth treatment and died of pulmonary edema and congestion. Two animals were sacrificed three days after the final treatment, and the remaining three were sacrificed seven days later. The first two had spleens that were large, dark, and congested, with foci of blood formation. Of the last three, two had congested spleens, one of which showed foci of blood formation.

Primary Irritation and Sensitization of the Skin

A 33 per cent water paste of 3-(m-chlorophenyl)-1,1-dimethylurea was practically non-irritating to the intact skin and mildly irritating to the broken skin of guinea pigs. No allergic skin sensitization was produced.

Summary

The ALD for 3-(m-chlorophenyl)-1,1-dimethylurea was found to be 7500 mg/kg when the compound was administered orally to rats. All the animals became weak, pale, and incoordinated. Sublethal doses produced an enlargement, darkening, and congestion of the spleen, with increased blood formation.

This compound was also found to produce cumulative toxicity, causing the death of one of six rats after the final treatment. Four of the survivors showed large, dark, and congested spleens, with foci of blood formation present.

A 33 per cent water paste of 3-(m-chlorophenyl)-1,1-dimethylurea was found to be non-irritating to intact skin, and mildly irritating to broken skin. It did not produce sensitization in guinea pigs.

Conclusions

The three isomers of 3-chlorophenyl-1,1-dimethylurea (o-, m- and p-) are of comparable acute toxicity.

The most marked cumulative toxic effects were caused by the ortho form; the meta form was almost as toxic; the para form, in spite of its definite effects, produced the least cumulative toxicity of the three.

It was found that 3-(p-chlorophenyl)-1,1-dimethylurea was the least irritating to intact and broken skin, while the ortho form was the most irritating. None of the three isomers was found to be a sensitizer.

TETRAMETHYLUREA

The proposed use of tetramethylurea as a catalyst in the manufacture of urea herbicides, as well as other possible industrial applications of this compound, made a preliminary investigation of its toxicity advisable. Acute and subacute oral toxicity and skin irritation and sensitization properties were studied, using a sample coded NB 2100-16 (Haskell No. 729). Details of these determinations are as follows:

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) of tetramethylurea was found to be 2250 mg/kg of body weight for male albino rats when the material was administered by stomach tube as a 20 or 40 per cent aqueous solution. The rats which received lethal doses showed marked discomfort, weight loss, and weakness. High lethal doses caused death within a few hours, while the lower ones proved fatal after several days. The only anatomical evidence of pathology was found in the liver, where variation in staining and in the size of nuclei suggested a focus of toxic action. Animals receiving sublethal doses showed an initial weight loss following treatment. They were sacrificed ten days after treatment. The liver of one rat showed evidence of recovery from toxic injury. The others showed no pathology.

Subacute Oral Toxicity

Doses of 450 mg/kg of body weight (one-fifth ALD) were administered orally to each of six male albino rats five times a week for two weeks. The animals lost weight during the treatments but regained over the week end and during the observation period. They were slightly pale and uncomfortable during treatment. Three rats were sacrificed on the third day following the final treatment; the remaining three were sacrificed on the tenth day. Autopsy revealed evidence of temporary injury to the kidneys and suggested minimal injury to the liver.

Primary Irritation and Sensitization of the Skin

Application of pure tetramethylurea to the intact skin of guinea pigs caused an immediate, but temporary, strong irritation. In original state or as a 50 per cent aqueous solution, this compound was moderately irritating to scratched skin. Intradermal injections of 0.1 ml of the material in saline caused mild irritation. The guinea pigs did not become sensitized to tetramethylurea.

Summary and Conclusions

The ALD for tetramethylurea was found to be 2250 mg/kg of body weight for rats when administered orally. Animals receiving sublethal doses showed a slight weight loss. The liver of one of these animals showed evidence of injury; the other animals showed no pathology. Lethal doses produced marked discomfort, weight loss, and weakness. The only anatomical evidence of pathology was found in the liver.

Repeated doses of tetramethylurea produced cumulative toxicity, injuring the kidneys and possibly the liver.

Tetramethylurea in its pure state was strongly irritating to intact skin and moderately irritating to abraded skin. It did not produce sensitization in guinea pigs.

The above data would indicate the advisability of handling tetramethylurea with reasonable care to avoid irritating the skin and to minimize the possibility of systemic effects.

3-(p-CHLOROPHENYL)-1,1-DIMETHYLUREA INTERMEDIATES: p-CHLOROPHENYLUREA AND p-CHLOROANILINE

The compound p-chlorophenylurea is an important intermediate in the manufacture of 3-(p-chlorophenyl)-1,1-dimethylurea. Since it would be handled extensively, an evaluation of its oral and skin toxicity was carried out. For these studies the technical product (Cleveland p-chlorophenylurea, Batch No. 2, Haskell No. 577) was used. It had a 93 per cent p-chlorophenylurea content, along with 6 per cent bis-(p-chlorophenyl)urea, a normal by-product. Similar determinations were made using p-chloroaniline, another 3-(p-chlorophenyl)-1,1-dimethylurea intermediate. The sample used (NB 1332-40, Haskell No. 811) had a 99.5 per cent assay. Details of the tests on both of these intermediates are as follows:

p-Chlorophenylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 2250 mg/kg of body weight for male albino rats when p-chlorophenylurea was administered by stomach tube as a 25 or 30 per cent suspension in peanut oil. All of the animals

showed discomfort, weakness, incoordination, and weight loss. Animals receiving sublethal doses were sacrificed ten to thirteen days after treatment. The animals receiving lethal doses died within one to three days. The pathogenesis for this group was not clear cut but might involve injury to the liver.

Subacute Oral Toxicity

Doses of 450 mg/kg of body weight (one-fifth ALD) were administered orally to each of six male albino rats five times a week for two weeks. The animals showed marked discomfort and weakness in their hind quarters. They were pale and slightly cyanotic during the first week of treatment. By the second week, discomfort and weakness were less marked and there was no cyanosis. Three rats were sacrificed three days after the final treatment. The remaining three were held until the tenth day, during which time they regained their original weights and continued to gain rapidly. Autopsies revealed that p-chlorophenylurea may cause a temporary injury to the liver. Increased hematopoiesis was also found in two of the three animals which were sacrificed three days after the final treatment.

Primary Irritation and Sensitization of the Skin

A 33 per cent suspension of p-chlorophenylurea in 1 per cent polyvinyl alcohol was practically non-irritating to the intact skin and mildly irritating to the abraded skin of guinea pigs. p-Chlorophenylurea did not produce allergic skin sensitization.

Summary

The ALD for p-chlorophenylurea was found to be 2250 mg/kg of body weight for rats when the material was administered orally. Discomfort, weakness, incoordination, and weight loss were observed in all animals treated. The pathogenesis for this group may involve injury to the liver.

Repeated doses of 450 mg/kg were found to produce liver damage and increased hematopoiesis in two of three animals sacrificed three days after the final treatment. Neither liver injury nor increased hematopoiesis was observed in animals which were sacrificed ten days after the final treatment. Thus, the cumulative toxic effect of p-chlorophenylurea would appear to be temporary.

A 33 per cent suspension of p-chlorophenylurea in 1 per cent polyvinyl alcohol was found to be neither a primary irritant nor a sensitizer when it was applied to the intact and abraded skin of guinea pigs.

p-ChloroanilineAcute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 200 mg/kg of body weight for male albino rats when the material was administered by stomach tube as a 5 or 10 per cent solution of p-chloroaniline in 3 per cent acetone-peanut oil. All of the animals became pale, cyanotic, and incoordinated. The higher doses caused more severe reactions than the lower doses. Doses exceeding 80 mg/kg produced marked weakness. Lethal doses caused death within one to seven days. Autopsy revealed that these animals suffered hepatitis and methemoglobinemia. The animals which received sublethal doses were sacrificed ten to seventeen days after treatment. Incomplete recovery from methemoglobinemia was the consistent diagnosis of the pathology found when these animals were autopsied.

Subacute Oral Toxicity

Doses of 40 mg/kg were administered orally to each of six male albino rats twelve times during a seventeen-day period. During the first week, the rats were pale, cyanotic, and incoordinated after treatment. The reaction to treatments the second week was similar but less severe. The third week the animals appeared in fairly good condition but remained pale. Blood counts showed a definite decrease in the number of red cells and amount of hemoglobin present as the treatment period progressed. The weights of the rats exceeded their original weights at the end of the treatment period. Three rats were sacrificed after the final treatment; the remaining three were held for a twelve-day observation period.

A record of the organ weights at the time of sacrifice shows that the spleens were very large immediately after the treatment period, but there was a tendency toward recovery in twelve days. Pathological examination revealed that those animals sacrificed after the final treatment showed a definite reaction to the methemoglobinemia produced by the p-chloroaniline. After a twelve-day observation period, however, there was almost complete recovery from the methemoglobinemia.

Primary Irritation and Sensitization of the Skin

A 33-per cent suspension of p-chloroaniline in 1 per cent polyvinyl alcohol was non-irritating to the intact skin of guinea pigs. A 10-per cent suspension was mildly irritating to broken skin. No allergic skin sensitization was produced by p-chloroaniline.

Summary and Conclusions

The ALD of p-chloroaniline was found to be 200 mg/kg of body weight for rats when the material was administered orally. Lethal doses produced hepatitis and methemoglobinemia. Sublethal doses also produced methemoglobinemia from which the animals had partially recovered at the end of a ten-day observation period.

Repeated doses of 40 mg/kg, given orally to rats, produced a definite decrease in the number and hemoglobin content of the red blood cells. Animals sacrificed after the final treatment showed a definite reaction to the methemoglobinemia which had been produced by the compound. After a twelve-day observation period there was almost complete recovery from the methemoglobinemia.

A 33 per cent suspension of p-chloroaniline was non-irritating to the intact skin, while a 10 per cent suspension was mildly irritating to the abraded skin of guinea pigs. No allergic skin sensitization was produced.

ANALOGS OF 3-(p-CHLOROPHENYL)-1,1-DIMETHYLUREA

1,1-Dimethyl-3-phenylurea

The oral toxicity was studied on an acute level by means of the ALD and LD₅₀ determinations and on a subacute level by means of the administration of repeated doses equal to one-fifth ALD as well as a feeding test. The problems of skin irritation and sensitization were also investigated. For these tests, a sample of 1,1-dimethyl-3-phenylurea, coded IN 12,895-1, H-1245-24 (Haskell No. 598) was used.

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 7500 mg/kg of body weight for male albino rats when 1,1-dimethyl-3-phenylurea was administered by stomach tube as a 30 per cent suspension in peanut oil. The lower sublethal doses caused no unusual clinical signs; the higher sublethal doses produced discomfort, labored respiration, weakness, and irritability. When these animals were sacrificed eight to thirteen days after treatment, no significant pathology was found. The lethal doses caused the same clinical signs as the high sublethal doses and proved fatal within a few hours. No definite pathology was found. The suggested pathogenesis was gastroenteritis, from which the animals receiving sublethal doses recovered.

The LD₅₀ is more precise than the ALD as an estimate of acute toxicity. For this determination, a series of dose levels, spaced at equal logarithmic intervals, was chosen. Five groups of ten male albino rats each received 1,1-dimethyl-3-phenylurea in peanut oil at the various dose levels. The LD₅₀, or dose that would kill 50 per cent of the animals, was calculated to be 6400 mg/kg, with confidence limits of 3560 to 11,520 mg/kg. The animals showed discomfort and weakness in the hind quarters after treatment. In addition, the higher doses produced pallor and cyanosis. When the animals were sacrificed two weeks after treatment, there was pathological evidence of gastritis. The animals which died showed comparable pathology.

Subacute Oral Toxicity

Doses of 1500 mg/kg (one-fifth ALD) were administered orally to each of six male albino rats five times a week for two weeks. The animals became irritable and weak and lost weight continuously as the treatments progressed. One animal died after the sixth treatment and another succumbed after the tenth. Both of these animals suffered gastric atony with possible liver damage. The four remaining animals were sacrificed ten days after the final treatment. At autopsy the spleens of all four showed foci of blood formation.

A feeding experiment was also conducted for a six-week period, during which time ten rats (five male and five female) were fed a diet of ground chow containing 0.05 per cent 1,1-dimethyl-3-phenylurea. No clinical signs of toxicity were observed. Blood counts taken at the end of one month were within the normal limits. The rats consumed 48 mg 1,1-dimethyl-3-phenylurea/kg/rat/day. When they were sacrificed at the end of the sixth week, no significant pathology was found.

Primary Irritation and Sensitization of the Skin

A 33 per cent aqueous paste of 1,1-dimethyl-3-phenylurea was found to be practically non-irritating to the intact skin and moderately irritating to the broken skin of guinea pigs. A 10 per cent solution in 1 per cent polyvinyl alcohol was very mildly irritating to the broken skin. 1,1-Dimethyl-3-phenylurea did not produce allergic skin sensitization in guinea pigs.

Summary

The ALD of 1,1-dimethyl-3-phenylurea was found to be 7500 mg/kg when the material was administered orally to rats. High sublethal doses as well as the lethal dose produced discomfort, labored respiration, weakness, and nervousness. The animals which received sublethal doses showed no significant pathology when they were sacrificed. The animals which died showed no definite pathology. The suggested pathogenesis was gastro-enteritis, from which the animals receiving sublethal doses recovered.

The LD₅₀ was found to be 6400 mg/kg, with confidence limits of 3560 to 11,520 mg/kg. Those receiving higher doses became pale and cyanotic. Pathological examination of those animals which died as well as those that were sacrificed revealed evidence of gastritis.

Repeated doses of 1500 mg 1,1-dimethyl-3-phenylurea/kg body weight produced weakness, irritability, and weight loss in rats. Two animals died during the two-week treatment period. Both suffered gastric atony with possible liver damage. When the four survivors were sacrificed, foci of blood formation were found in the spleens.

During a six-week feeding experiment, six rats were fed a diet of ground dog chow containing 0.05 per cent 1,1-dimethyl-3-phenylurea. They

received an average of 48 mg/kg/rat/day. The rats showed no abnormal clinical signs and their hematology was normal. When they were sacrificed, no significant pathology was found.

A 33 per cent aqueous paste of 1,1-dimethyl-3-phenylurea was non-irritating to intact skin and moderately irritating to broken skin. A 10 per cent solution was mildly irritating to broken skin. 1,1-Dimethyl-3-phenylurea did not produce sensitization in guinea pigs.

3-(p-Methoxyphenyl)-1,1-dimethylurea

The acute oral toxicity of 3-(p-methoxyphenyl)-1,1-dimethylurea was investigated using the ALD and LD₅₀ determinations. Subacute oral toxicity and skin irritation and sensitization were also studied. For most of these tests, a pure sample of 3-(p-methoxyphenyl)-1,1-dimethylurea coded IN 14,741-1, H 1245-115 (Haskell No. 583) was used. For the LD₅₀ determination, however, a second sample, coded H 1245-161, was used.

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 1500 mg/kg of body weight for male albino rats when 3-(p-methoxyphenyl)-1,1-dimethylurea was administered by stomach tube as a 20 or 25 per cent suspension in 15 per cent acetone-peanut oil. The animals became weak and uncomfortable. Sublethal doses produced incoordination, while lethal doses caused paralysis of the hind quarters. The animals which survived treatment showed no pathology when they were autopsied on the thirteenth day. The animals which died suffered pulmonary congestion and edema. No consistent pathology was demonstrated by this group.

For a more precise estimate of the acute oral toxicity of 3-(p-methoxyphenyl)-1,1-dimethylurea, the LD₅₀ was determined. For this, a series of dose levels, at equal logarithmic intervals, was chosen. Four groups of ten rats each were treated with 3-(p-methoxyphenyl)-1,1-dimethylurea at the selected dose levels. The LD₅₀, or dose that would kill 50 per cent of the animals, was then calculated to be 1750 mg/kg with confidence limits of 1460 to 2100 mg/kg. The animals which survived treatment showed no pathology when they were sacrificed two weeks later. Those animals which died, however, showed evidence of gastritis, probably hepatitis, and possibly nephritis.

Subacute Oral Toxicity

Doses of 300 mg/kg (one-fifth ALD) were administered orally to each of six male albino rats five times a week for two weeks. The animals showed slight discomfort after the tenth treatment, but no other clinical signs were observed. Three animals were sacrificed on the third day of observation; the remaining three were sacrificed on the tenth day. No consistent pathology was found, but there were several indications of kidney damage.

Primary Irritation and Sensitization of the Skin

A 33 per cent aqueous paste of 3-(p-methoxyphenyl)-1,1-dimethylurea was found to be practically non-irritating to the intact and abraded skin of guinea pigs. It did not produce allergic skin sensitization.

Summary

The ALD of 3-(p-methoxyphenyl)-1,1-dimethylurea was found to be 1500 mg/kg when it was administered orally to rats. Discomfort, weakness, and incoordination developed. Lethal doses produced paralysis of the hind quarters. Survivors showed no pathology when they were sacrificed. No consistent pathology was demonstrated by the group which died.

The LD₅₀ of 3-(p-methoxyphenyl)-1,1-dimethylurea was calculated to be 1750 mg/kg with confidence limits of 1460 to 2100 mg/kg. Survivors showed no pathology when they were sacrificed. The animals that died, however, showed evidence of gastritis, probably hepatitis, and possibly nephritis.

Repeated doses of 300 mg/kg produced no unusual clinical signs and no consistent pathology. There were, however, several indications of kidney damage.

A 33 per cent aqueous paste of 3-(p-methoxyphenyl)-1,1-dimethylurea was non-irritating to the intact and broken skin of guinea pigs. The animals did not become sensitized to this chemical.

3-(3,4-Dichlorophenyl)-1,1-dimethylurea

This compound, 3-(3,4-dichlorophenyl)-1,1-dimethylurea, showed excellent herbicidal properties. It was therefore necessary to evaluate its toxicity and compare the data with that obtained for the p-chlorophenyl compound. Using the submitted sample (IN 14,740-3, H-1309-4; Haskell No. 624), the acute and chronic oral toxicity for rats as well as the skin irritation and sensitization tests on guinea pigs were determined. The ninety-day feeding test was carried out using a 98 per cent pure sample of 3-(3,4-dichlorophenyl)-1,1-dimethylurea coded NB 2643-5-1 (Haskell No. 1021). Details of these studies follow:

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) for male albino rats was found to be 5000 mg/kg of body weight when a 30 per cent suspension of 3-(3,4-dichlorophenyl)-1,1-dimethylurea in peanut oil containing 15 per cent acetone was administered by stomach tube. Animals receiving sublethal doses showed discomfort and slight incoordination after treatment. When these rats were sacrificed twelve to thirteen days later their spleens appeared large, dark, and congested, with numerous foci of blood formation in all cases. The suggested pathogenesis was blood destruction with compensatory erythropoiesis. The animals receiving lethal doses died within twenty hours. They showed

marked discomfort and incoordination after treatment. Within a few hours they were unable to move and had a very rapid heart rate. Autopsy revealed pulmonary edema and congestion.

The LD₅₀ was also determined for this compound. For this test, a series of dose levels, spaced at equal logarithmic intervals, was chosen. Five groups, each consisting of ten male albino rats, received the calculated dosage of 3-(3,4-dichlorophenyl)-1,1-dimethylurea in peanut oil. The LD₅₀, or dose that would kill 50 per cent of the animals, was calculated to be 3400 mg/kg of body weight with confidence limits of 2900 to 4000 mg/kg. All the animals showed discomfort, weakness, labored respiration, lacrimation, and cyanosis. The animals which died lost weight continually; the survivors began to regain weight about a week after treatment. Autopsies were performed on a few of the survivors which had been sacrificed. The suggested pathogenesis was blood destruction and methemoglobinemia with compensatory red blood cell formation.

Subacute Oral Toxicity

Doses of 1000 mg/kg (one-fifth ALD) were administered orally to each of six male albino rats five times a week for two weeks. During the treatment period the animals were pale and uncomfortable and did not gain weight. Three rats were sacrificed and autopsied three days after the final treatment. The spleens were large, dark, and congested. There were foci of blood formation in both the spleen and the bone marrow. The three remaining rats were sacrificed eleven days after the final treatment. One of the three had a dark, enlarged, and congested spleen, and two of the animals showed foci of blood formation. In all three cases, the spleen contained groups of dark brown granules (hemosiderin). The pallor of the animals and the hemosiderosis of the spleen indicated probable red blood cell destruction. The erythropoiesis was a compensatory mechanism.

Ninety-Day Feeding Test

Three groups of rats, each consisting of five males and five females, were fed a known amount of 3-(3,4-dichlorophenyl)-1,1-dimethylurea in ground chow. Their food and water consumption and weight records were compared with those of the control male and female rats. The three test groups received 0.005, 0.05, and 0.5 per cent 3-(3,4-dichlorophenyl)-1,1-dimethylurea, respectively. Blood samples were taken before the animals were sacrificed. Blood counts are shown in Table II. The experiment terminated in about ninety days.

Both the male and female rats receiving 0.005 per cent 3-(3,4-dichlorophenyl)-1,1-dimethylurea gained almost as much weight and consumed almost as much food as did the controls. No clinical signs were observed, and no pathology was found when they were sacrificed.

The male rats receiving 0.05 per cent 3-(3,4-dichlorophenyl)-1,1-dimethylurea compared favorably with the control animals in weight gain and food and water consumption. The females gained less weight and consumed

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TABLE II

BLOOD COUNTS - 3-(3,4-DICHLOROPHENYL)-1,1-DIMETHYLUREA RATS - THREE MONTHS

	RBC	WBC	Hbg	Differential			
				P	L	M E	
Control Group							
Male	8,428,000	10,950	11.4	12	83	0	5
Female	8,152,000	11,175	11.4	10	88	0	2
0.5% 3-(3,4-dichlorophenyl)-1,1-dimethylurea							
Male	6,693,000	17,180	10.4	6	92	0	2
Female	5,768,000	12,920	10.3	8	90	0	1
0.05% 3-(3,4-dichlorophenyl)-1,1-dimethylurea							
Male	8,417,000	16,950	12.4	5	92	0	3
Female	7,352,000	16,380	10.5	7	92	0	1
0.005% 3-(3,4-dichlorophenyl)-1,1-dimethylurea							
Male	8,414,000	12,540	12.2	4	95	0	1
Female	8,207,000	15,580	11.2	9	89	0	2

Key: RBC - red blood cells
WBC - white blood cells
Hbg - hemoglobin
P - polymorphonuclear leucocytes
L - lymphocytes
M - monocytes
E - eosinophils

less food than the controls. They also appeared cyanotic. In spite of these clinical signs of methemoglobinemia in the females, autopsy revealed no significant pathology in either sex.

The rats receiving 0.5 per cent 3-(3,4-dichlorophenyl)-1,1-dimethylurea were pale and cyanotic during most of the experiment. Their growth rate was steady, but much lower than the controls for both sexes. Their food consumption was also lower. Blood samples showed slightly abnormal hematology. When the animals were sacrificed and autopsied, chronic methemoglobinemia was a consistent finding. Clinically it was characterized by cyanosis. Pathologically it was indicated by the brown color of the blood and organs. Enlargement of the spleen, hemosiderosis, and increased blood formation were also found.

Primary Irritation and Sensitization of the Skin

A 50 per cent water paste of 3-(3,4-dichlorophenyl)-1,1-dimethylurea was found to be non-irritating to the intact skin and moderately irritating to the broken skin of guinea pigs. Mild irritation of broken skin was caused by a 10 per cent aqueous suspension. 3-(3,4-Dichlorophenyl)-1,1-dimethylurea did not produce allergic skin sensitization.

Summary and Conclusions

The AID of 3-(3,4-dichlorophenyl)-1,1-dimethylurea was found to be 5000 mg/kg of body weight when administered orally to male albino rats. Sublethal doses caused weakness and incoordination. Pathological evidence of blood destruction and/or methemoglobinemia was found. Lethal doses produced prompt death from pulmonary edema. Some liver and kidney damage was also apparent.

The LD₅₀ was calculated to be 3400 mg/kg of body weight, with confidence limits of 2900 to 4000 mg/kg. The suggested pathogenesis was blood destruction and methemoglobinemia, with compensatory red blood cell formation.

Repeated doses of 1000 mg/kg caused some cumulative toxicity. The animals which were sacrificed two days after the final treatment showed evidence of compensatory blood formation. The animals sacrificed eleven days after the treatment showed hemosiderosis of the spleen, which would indicate blood destruction.

The ninety-day feeding test revealed that a dose of 0.005 per cent 3-(3,4-dichlorophenyl)-1,1-dimethylurea in the food consumed caused no apparent harm to rats. The females receiving 0.05 per cent 3-(3,4-dichlorophenyl)-1,1-dimethylurea showed clinical signs of methemoglobinemia, but the males were unaffected. Both the males and females receiving 0.5 per cent 3-(3,4-dichlorophenyl)-1,1-dimethylurea showed clinical and pathological evidence of chronic methemoglobinemia.

A 50 per cent water paste of 3-(3,4-dichlorophenyl)-1,1-dimethylurea produced no irritation of intact skin and moderate irritation of broken skin of guinea pigs. It is not a sensitizer.

As in the case of 3-(p-chlorophenyl)-1,1-dimethylurea, it would appear that a moderate amount of skin contact with 3-(3,4-dichlorophenyl)-1,1-dimethylurea would not be harmful because the material is non-irritant and not a sensitizer. On the other hand, due care must be taken when handling 3-(3,4-dichlorophenyl)-1,1-dimethylurea because of its cumulative oral toxicity. Its toxic action is similar to that of 3-(p-chlorophenyl)-1,1-dimethylurea, producing blood destruction and methemoglobinemia.

3-(3,4-DICHLOROPHENYL)-1,1-DIMETHYLUREA INTERMEDIATES: 3,4-DICHLOROANILINE AND 3,4-DICHLOROPHENYLUREA

Two intermediates involved in the manufacture of 3-(3,4-dichlorophenyl)-1,1-dimethylurea are 3,4-dichloroaniline and 3,4-dichlorophenylurea. It is therefore desirable to have the preliminary oral and skin toxicity evaluation for both of these compounds. The dichloroaniline sample was pure, but the 3,4-dichlorophenylurea contained approximately 18 per cent 1,3-bis-(3,4-dichlorophenyl)urea and 4 per cent dichloroaniline. 3,4-Dichlorophenylurea of this composition would normally be handled in the plant. The dichloroaniline sample (11-9-51, Gerjovich) was designated Haskell No. 730. The 3,4-dichlorophenylurea sample (2098-38, No. 4) was designated Haskell No. 731.

3,4-Dichloroaniline

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 670 mg/kg of body weight for male albino rats when 3,4-dichloroaniline was administered by stomach tube as a 10 per cent solution in peanut oil. All of the animals showed some discomfort after treatment. The higher doses produced general weakness, diarrhea, and cyanosis. The blood and organs of those animals which died were red-brown, indicating death from acute methemoglobinemia. When the survivors were sacrificed ten days after treatment, they showed evidence of having had methemoglobinemia: the spleens were large, dark, and congested; and increased blood formation was found in the spleen and bone marrow.

Subacute Oral Toxicity

Doses of 134 mg/kg (one-fifth ALD) were given orally to each of six male albino rats five times a week for two weeks. During this treatment period, the animals were uncomfortable, somewhat weak, and slightly cyanotic. Body weights were practically unaffected.

Three rats were sacrificed on the third day after the final treatment; the remaining three were sacrificed on the tenth day. The spleens of the latter group were somewhat large and dark, but the enlargement was not as marked as that noted in the first group. Erythropoiesis was also more marked in the first group. The animals sacrificed on the third day thus showed partial recovery from methemoglobinemia, while those sacrificed on the tenth day showed almost complete recovery.

Primary Irritation and Sensitization of the Skin

A 33 per cent aqueous paste of 3,4-dichloroaniline was non-irritating to the unbroken skin of young guinea pigs, but was mildly irritating to the intact skin of old pigs. A 10 per cent suspension of 3,4-dichloroaniline in 1 per cent polyvinyl alcohol was mildly irritating to the abraded skin of both young and old guinea pigs. Repeated applications of this material produced an allergic skin sensitization in guinea pigs.

Summary

The ALD for 3,4-dichloroaniline was found to be 670 mg/kg for rats when the material was administered orally. All levels tested produced methemoglobinemia, from which recovery was possible at the lower dose levels. A compensatory erythropoiesis was noted in all cases when the survivors were sacrificed. Animals receiving lethal doses died of acute methemoglobinemia.

Repeated doses of 134 mg/kg (one-fifth ALD) given orally also produced methemoglobinemia in rats. Those animals which were sacrificed on the third day after the final treatment had partially recovered, while those sacrificed on the tenth day showed almost complete recovery from the methemoglobinemia.

A 33 per cent aqueous paste of 3,4-dichloroaniline was practically non-irritating to the intact skin of guinea pigs. A 10 per cent suspension in polyvinyl alcohol was mildly irritating to abraded skin. 3,4-Dichloroaniline is definitely a skin sensitizer.

3,4-Dichlorophenylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 1000 mg/kg of body weight for male albino rats when dichlorophenylurea was given by stomach tube as a 20 per cent suspension in peanut oil. The animals became weak and incoördinate. Higher doses produced unconsciousness. Those animals which survived treatment were sacrificed ten to eleven days later. In spite of the severe clinical signs observed, no pathology was found in these survivors. Lethal doses, however, produced damage to the liver and/or the kidneys. It is therefore possible that sublethal doses may cause temporary damage to the liver and kidneys.

Subacute Oral Toxicity

Doses of 200 mg/kg (one-fifth ALD) were administered orally to each of six male albino rats five times a week for two weeks. There was a marked initial weight loss which was almost regained by the end of the treatment and observation periods. The reactions to the first dose were marked discomfort, weakness, and incoordination. Subsequent doses caused similar but less severe reactions. The three animals which were sacrificed three days after the final treatment showed evidence of liver damage. Of the three animals which were sacrificed ten days after the final treatment, two showed no pathology. The third showed evidence of regeneration from kidney injury.

Primary Irritation and Sensitization of the Skin

A 33 per cent aqueous paste of dichlorophenylurea produced moderate irritation when applied to the intact skin of guinea pigs. A 10 per cent suspension was also moderately irritating to abraded skin. After repeated applications, the irritation caused by dichlorophenylurea was greater, indicating skin sensitization. The same set of guinea pigs then received the sensitizing treatments with 3-(3,4-dichlorophenyl)-1,1-dimethylurea, but no cross-sensitization was produced. It is possible that the 4 per cent dichloroaniline in the dichlorophenylurea sample caused the sensitization of this group of guinea pigs, for dichloroaniline alone has been found to produce sensitization. The application of dichlorophenylurea to the skin of guinea pigs already sensitized to 3,4-dichloroaniline indicated that dichlorophenylurea of this degree of purity is a potential sensitizer.

Summary

The ALD was found to be 1000 mg/kg of body weight when dichlorophenylurea was given orally to rats. Sublethal doses produced weakness and incoordination, but no pathology was found when these animals were sacrificed ten days after treatment. Lethal doses caused marked weakness, incoordination, and unconsciousness. Autopsy revealed damage to the liver and possibly the kidneys. It is possible that sublethal doses cause similar, but temporary, injuries.

Repeated oral doses of 200 mg/kg produced weakness, discomfort, and incoordination in rats. Three animals were sacrificed three days after the final treatment and showed evidence of liver damage. When the three remaining animals were sacrificed ten days after the final treatment, two showed no pathology; the third showed evidence of regeneration from kidney injury.

The application of dichlorophenylurea as a 33 per cent aqueous paste on intact skin and a 10 per cent suspension on abraded skin produced moderate irritation. Dichlorophenylurea was found to be a potential skin sensitizer for guinea pigs, but sensitization may have been due to the 4 per cent of 3,4-dichloroaniline present in the sample.

ANALOGS OF 3-(3,4-DICHLOROPHENYL)-1,1-DIMETHYLUREA

The following analogs of 3-(3,4-dichlorophenyl)-1,1-dimethylurea were submitted for preliminary oral toxicity studies:

- 1-(3,4-dichlorophenyl)-1,3,3-trimethylurea (Haskell No. 1180)
- 1-(3,4-dichlorophenyl)-3-methylurea (IN 15,654-5; NB 2637-31; Haskell No. 1029)
- 3-(3,4-dichlorophenyl)-1,1-diethylurea (IN 15,624-1; NB 2126-190; Haskell No. 1026)
- 3-(3,4-dichlorophenyl)-1-methyl-1-isopropylurea (IN 16,386; NB 2126-151; Haskell No. 1027)
- 3-(3,4-dichlorophenyl)-1-methyl-1-sec-butylurea (IN 16,393-2; NB 2637-1; Haskell No. 1028)

Acute oral toxicity, as estimated by the Approximate Lethal Dose, was determined for all four compounds. An LD₅₀ was also determined using 1-(3,4-dichlorophenyl)-3-methylurea. Subacute oral tests were done using 1-(3,4-dichlorophenyl)-3-methylurea and 3-(3,4-dichlorophenyl)-1,1-diethylurea.

1-(3,4-Dichlorophenyl)-1,3,3-trimethylureaAcute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 1500 mg/kg of body weight for male albino rats when the material was administered by stomach tube as a 20 per cent suspension in peanut oil. Lethal doses produced marked weakness and discomfort and slow, irregular respiration. The animals died overnight, but the pathogenesis was not apparent. The animal which received 1000 mg/kg was markedly ill but survived. Lower doses produced no clinical signs. When these animals were sacrificed nine to ten days after treatment, two of them showed numerous foci of blood formation in the spleen, the significance of which is not understood.

Subacute Oral Toxicity

Daily doses of 300 mg/kg were administered ten times to each of six male albino rats. The animals showed a marked initial weight loss but improved during the second week. During the last five treatments, slight salivation and pallor were noted. Three of the rats were sacrificed after the tenth treatment; the other three were sacrificed ten days later. No significant pathology was found, although one animal showed evidence of ectopic blood formation.

Summary

1-(3,4-Dichlorophenyl)-1,3,3-trimethylurea is a slightly toxic compound, the ALD being 1500 mg/kg. Lethal doses were rapidly fatal, but the pathogenesis was not apparent.

Ten repeated doses of 300 mg/kg produced no cumulative toxicity. Although the growth rate was retarded, no significant pathology was found when the animals were sacrificed.

The numerous foci of blood formation in the spleens of three test animals may be coincidental to the experiments. More extensive feeding tests would be required to determine whether or not these effects were significant and were definitely related to the chemical ingested.

1-(3,4-Dichlorophenyl)-3-methylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 3400 mg/kg when 1-(3,4-dichlorophenyl)-3-methylurea was administered by stomach tube to male albino rats as a 25 or 30 per cent suspension in peanut oil. Doses of 1000 mg/kg up to 7500 mg/kg produced marked discomfort and weakness. Lethal doses caused unconsciousness. Within a week after treatment, rats receiving sublethal doses had recovered from the clinical effects of the compound. These survivors were sacrificed eleven days after treatment. Autopsy of all the rats revealed no significant pathology.

To gain a more accurate estimate of the acute oral toxicity of this compound, the LD₅₀ was determined. By selecting eight dose levels at equal logarithmic intervals, the dose that would kill 50 per cent of the rats was calculated to be 1600 mg/kg, with confidence limits of 2030 and 1260 mg/kg. This value is much lower than the LD₅₀ for either 3-(p-chlorophenyl)-1,1-dimethylurea or 3-(3,4-dichlorophenyl)-1,1-dimethylurea, indicating that 1-(3,4-dichlorophenyl)-3-methylurea is more toxic than the other two compounds.

Subacute Oral Toxicity

Doses of 680 mg/kg were administered orally to each of six male albino rats five times a week for two weeks. All of these animals showed marked cyanosis, incoordination, weakness, and nervousness. Three animals died during the treatment period. Autopsies showed gastritis and possible liver damage in all three cases. The spleens were also large and congested, and foci of blood formation were present. One of the surviving rats was sacrificed after the tenth treatment. This spleen was also dark and congested, with numerous foci of blood formation. These cases of increased erythropoiesis were probably the result of blood destruction. When the two remaining rats were sacrificed ten days after the final treatment, no pathology was found, indicating complete recovery from the blood destruction.

Summary

The ALD was found to be 3400 mg/kg when 1-(3,4-dichlorophenyl)-3-methylurea was administered orally to rats. In spite of clinical signs such as discomfort and weakness, no pathological evidence of chemical injury was found. The LD₅₀ was found to be 1600 mg/kg, with confidence limits of 2030 and 1260 mg/kg.

Repeated doses of 680 mg/kg produced temporary toxic injury to the stomach, liver, and red blood cells.

3-(3,4-Dichlorophenyl)-1,1-diethylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to be 5000 mg/kg when 3-(3,4-dichlorophenyl)-1,1-diethylurea was administered by stomach tube to male albino rats as a 25 per cent suspension in peanut oil. Doses exceeding 1500 mg/kg produced marked discomfort and weakness. High doses brought rapid death from gastro-enteritis. Lower doses gave no evidence of residual gastro-enteritis when the animals were sacrificed ten days after treatment. There was evidence, however, of increased erythropoiesis, indicating the possibility of blood destruction.

Subacute Oral Toxicity

Doses of 1000 mg/kg were administered orally to each of six male albino rats five times a week for two weeks. After the first week of treatment, the animals showed discomfort, weakness, and cyanosis. These symptoms persisted throughout the second week of treatment. Their urine appeared quite brown. Some cyanosis was still evident four days after the final treatment. Three animals were sacrificed after the final treatment. All showed compensatory erythropoiesis. Another animal died of a coincidental lung abscess on the third day of observation. When the two remaining animals were sacrificed ten days after the final treatment, no significant pathology was found.

Summary

The ALD was found to be 5000 mg/kg when the material was administered orally to rats. High doses produced death from gastro-enteritis. Repeated doses of 1000 mg/kg also produced temporary compensatory erythropoiesis.

3-(3,4-Dichlorophenyl)-1-isopropyl-1-methylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to exceed 7500 mg/kg when 3-(3,4-dichlorophenyl)-1-isopropyl-1-methylurea was administered by stomach tube as a 20 or 30 per cent suspension in peanut oil to male albino

rats. No clinical signs were observed. When the animals were sacrificed ten days after treatment, there was no significant pathology. Since this compound produced no apparent toxic effects, no further tests were required.

3-(3,4-Dichlorophenyl)-1-sec-butyl-1-methylurea

Acute Oral Toxicity

The Approximate Lethal Dose (ALD) was found to exceed 11,000 mg/kg when 3-(3,4-dichlorophenyl)-1-sec-butyl-1-methylurea was administered by stomach tube as a 30 per cent suspension in peanut oil to male albino rats. No clinical signs were observed. When the rats were sacrificed ten days after treatment, no pathology attributable to the test chemical was found. Further tests were not required for this compound.

THE TOXICITY OF THE UREA HERBICIDES, INTERMEDIATES, AND CATALYSTS (SUMMARY)

A brief resume' of the toxicity tests is given in Tables III and IV.

Acute Oral Toxicity

None of the compounds in the group tested proved to be very toxic when single doses were given orally. The two aniline intermediates, p-chloroaniline and 3,4-dichloroaniline, are moderately toxic, the ALD values being 200 and 670 mg/kg, respectively. The other intermediates, p-chlorophenylurea and 3,4-dichlorophenylurea, and the catalyst, tetramethylurea, are slightly toxic.

Most of the urea herbicides are classified as slightly toxic because the ALD and/or LD₅₀ values are above 1000 and below 5000 mg/kg. In this group are: 3-(p-chlorophenyl)-1,1-dimethylurea; 3-(3,4-dichlorophenyl)-1,1-dimethylurea; 3-(o-chlorophenyl)-1,1-dimethylurea; 3-(p-methoxyphenyl)-1,1-dimethylurea; 1-(3,4-dichlorophenyl)-1,3,3-trimethylurea; 1-(3,4-dichlorophenyl)-3-methylurea; and 3-(3,4-dichlorophenyl)-1,1-diethylurea.

The remaining urea compounds are practically nontoxic: 3-(m-chlorophenyl)-1,1-dimethylurea; 1,1-dimethyl-3-phenylurea; 3-(3,4-dichlorophenyl)-1-isopropyl-1-methylurea; and 3-(3,4-dichlorophenyl)-1-sec-butyl-1-methylurea.

Subacute Oral Toxicity

When doses equal to one-fifth of the ALD were administered ten times, the following compounds were found to produce fatally cumulative toxic effects in at least one of the six test animals: 3-(p-chlorophenyl)-1,1-dimethylurea; 3-(o-chlorophenyl)-1,1-dimethylurea; 3-(m-chlorophenyl)-1,1-dimethylurea; 1,1-dimethyl-3-phenylurea; and 1-(3,4-dichlorophenyl)-3-methylurea.

Toxic effects resulting in pathology but no fatalities were produced by repeated doses of: 3-(3,4-dichlorophenyl)-1,1-dimethylurea; 3-(3,4-dichlorophenyl)-1,1-diethylurea; tetramethylurea; p-chlorophenylurea; p-chloroaniline; 3,4-dichloroaniline; and 3,4-dichlorophenylurea. At least partial recovery from toxic effects was noted ten days after the final treatment with each compound.

Repeated doses of 1-(3,4-dichlorophenyl)-1,3,3-trimethylurea produced no pathological evidence of cumulative toxicity. The cumulative toxic effects of 3-(3,4-dichlorophenyl)-1-isopropyl-1-methylurea and 3-(3,4-dichlorophenyl)-1-sec-butyl-1-methylurea were not determined because both compounds were practically nontoxic when given in single large doses.

Short-term feeding tests using 3-(p-chlorophenyl)-1,1-dimethylurea, 3-(3,4-dichlorophenyl)-1,1-dimethylurea, and 1,1-dimethyl-3-phenylurea were carried out. Dietary levels of 0.005, 0.05, and 0.5 per cent 3-(p-chlorophenyl)-1,1-dimethylurea produced some methemoglobinemia at the two lower levels and definite methemoglobinemia at the highest level when fed to rats for six weeks. The same dietary levels of 3-(3,4-dichlorophenyl)-1,1-dimethylurea, when fed to rats for three months, produced definite methemoglobinemia at the highest level only. Feeding 1,1-dimethyl-3-phenylurea as 0.05 per cent of the diet for six weeks produced no toxic effects.

Primary Irritation and Sensitization of the Skin

Of the eleven compounds tested, only two showed sensitization properties: 3,4-dichloroaniline is a strong sensitizer, while 3,4-dichlorophenylurea may be a potential sensitizer.

The only compound which was found to be a strong primary irritant was tetramethylurea.

The following compounds were relatively non-irritating to intact skin, were mildly irritating to abraded skin, and were not sensitizers: 3-(3,4-dichlorophenyl)-1,1-dimethylurea; 3-(o-chlorophenyl)-1,1-dimethylurea; 3-(m-chlorophenyl)-1,1-dimethylurea; 1,1-dimethyl-3-phenylurea; p-chlorophenylurea; and p-chloroaniline.

Neither 3-(p-chlorophenyl)-1,1-dimethylurea nor 3-(p-methoxyphenyl)-1,1-dimethylurea produced any irritation or sensitization.

The five remaining compounds were not tested for skin effects.

Conclusions

None of the urea herbicides tested proved to be very toxic under acute conditions. With the possible exception of 1-(3,4-dichlorophenyl)-1,3,3-trimethylurea, however, all of them produced some cumulative toxic effects.

Triage of 8(e) Submissions

Date sent to triage: _____

NON-CAP

CAP

Submission number: 12372A

TSCA Inventory:

Y

N

D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO

AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX

SBTOX

SEN

w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX

CTOX

EPI

RTOX

GTOX

STOX/ONCO

CTOX/ONCO

IMMUNO

CYTO

NEUR

Other (FATE, EXPO, MET, etc.): MET

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: 0 1 2 pages 119 pages _____

Notes:

Contractor reviewer: JW Date: 11/17/96

CECATS DATA: Submission # BEHO-1092-12372 SEQ. A
TYPE: INT. SUPP FLWP
SUBMITTER NAME: E. I. Dupont de Nemours and Company

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL. ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)
DISPOSITION:
0509 REFER TO CHEMICAL SCREENING
0570 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED (ADMIN HWAY)
0403 NOTIFICATION (H. WORKING WITH HQ)
0404 LAB/MSDS (TECHNICAL)
0405 PROCESS/AND/ING (TECHNICAL)
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 03/14/95

CHEMICAL NAME: See attached
CASE: _____

INFORMATION TYPE:	P.F.C.	INFORMATION TYPE:	P.F.C.	INFORMATION TYPE:	P.F.C.
0201 ONCO (HUMAN)	01 02 04	0216 EPICLIN	01 02 04	0241 IMMUNO (ANIMAL)	01 02 04
0202 ONCO (ANIMAL)	01 02 04	0217 HUMAN EXPOS (PROD CONTAM)	01 02 04	0242 IMMUNO (HUMAN)	01 02 04
0203 CEL I. TRANS (IN VITRO)	01 02 04	0218 HUMAN EXPOS (ACCIDENTAL)	01 02 04	0243 CHEMPHYS PROP	01 02 04
0204 MUTA (IN VITRO)	01 02 04	0219 HUMAN EXPOS (MONITORING)	01 02 04	0244 CLASTO (IN VITRO)	01 02 04
0205 MUTA (IN VIVO)	01 02 04	0220 ECOAQUA TOX	01 02 04	0245 CLASTO (ANIMAL)	01 02 04
0206 REPRO/TERATO (HUMAN)	01 02 04	0221 ENV. OCCUREL/FATE	01 02 04	0246 CLASTO (HUMAN)	01 02 04
0207 REPRO/TERATO (ANIMAL)	01 02 04	0222 EMER INCI OF ENV CONTAM	01 02 04	0247 DNA DAM/REPAIR	01 02 04
0208 NEURO (HUMAN)	01 02 04	0223 RESPONSE REQEST DELAY	01 02 04	<u>0248</u> PRODUSE/PROC	01 02 04
<u>0209</u> NEURO (ANIMAL)	01 02 04	0224 PROD/COMP/CHEM ID	01 02 04	0251 MSDS	01 02 04
0210 ACUTE TOX. (HUMAN)	01 02 04	0225 REPORTING RATIONALE	01 02 04	0259 OTHER	01 02 04
0211 CHR. TOX. (HUMAN)	01 02 04	0226 CONFIDENTIAL	01 02 04		
<u>0212</u> ACUTE TOX. (ANIMAL)	01 02 04	0227 ALLERG (HUMAN)	01 02 04		
<u>0213</u> SUB ACUTE TOX (ANIMAL)	01 02 04	<u>0228</u> ALLERG (ANIMAL)	01 02 04		
<u>0214</u> SUB CHRONIC TOX (ANIMAL)	01 02 04	<u>0229</u> METAB/PHARMACO (ANIMAL)	01 02 04		
0215 CHRONIC TOX (ANIMAL)	01 02 04	0240 METAB/PHARMACO (HUMAN)	01 02 04		

<u>TRIAGE DATA:</u>	<u>NON-CBI INVENTORY</u>	<u>ONGOING REVIEW</u>	<u>SPECIES</u>	<u>TOXICOLOGICAL CONCERN:</u>	<u>USE:</u>	<u>PRODUCTION:</u>
<u>CAS SR</u>	<u>YES</u>	<u>YES (DROP/REFER)</u>	<u>RAT</u>	<u>LOW</u>	<u>Herbicides</u>	<u>1954 (studies)</u>
	<u>NO</u>	<u>NO (CONTINUE)</u>	<u>GP</u>	<u>MED</u>	<u>Intermediate</u>	
	<u>IN IT-AMIN</u>	<u>REFER</u>	<u>RBT</u>	<u>HIGH</u>	<u>Catalyst</u>	
			<u>DOG</u>			

UNCLASSIFIED Herbicides - chlorophenyl-urea like compounds (8 chemicals) were tested orally for acute short duration tests with rats, guinea pigs, rabbits & dogs. Most of them were non-essitant & produced in coordination/weakness in hindquarters. Analyses containing compounds produced cyanosis & methemoglobinemia. Most of these chemicals were of moderate toxicity.

8046-1092-12372

CAS# 587-34-8; 582-44-5; 140-38-5; 632-22-4;
106-47-8; 95-76-1

CHEM: ① 3-(o-chlorophenyl)-1,1-dimethylurea; 582-44-5
② 3-(m-chlorophenyl)-1,1-dimethylurea; 587-34-8
③ tetramethylurea; ④ p-chlorophenylurea; 140-38-5
⑤ p-chloroaniline; ⑥ 1,1-dimethyl-3-phenylurea; 101-42-8
⑦ 3-(p-methoxyphenyl)-1,1-dimethylurea;
2327-02 ⑧ 3,4-dichlorophenylurea; 3,4-dichloroaniline; 95-76-1
Unknown ⑨ 1-(3,4-dichlorophenyl)-1,3,3-trimethylurea;
Unknown ⑩ 1-(3,4-dichlorophenyl)-3-methylurea;
Unknown ⑪ 3-(3,4-dichlorophenyl)1,1-diethylurea;
Unknown ⑫ 3-(3,4-dichlorophenyl)-1-methyl-1-isopropylurea;
Unknown ⑬ 3-(3,4-dichlorophenyl)1-methyl-1-sec-butylurea

TITLE: Toxicity of Urea Herbicides, Intermediates
and Catalysts

⑮ 3-(p-chlorophenyl)-
1,1-dimethylurea

DATE: 8/27/54

SUMMARY OF EFFECTS:

⑯ 3-(3,4-dichlorophenyl)-1,1-dimethylurea

- ORAL ALD/subacute 3-(o-chlorophenyl)-1,1-dimethylurea - incoordination
- ORAL ALD/subacute 3-(m-chlorophenyl)-1,1-dimethylurea - incoordination
- tetramethylurea - nothing to report
- ORAL ALD/subacute p-chlorophenylurea - incoordination/weakness in hindquarters
- ORAL ALD/subacute p-chloroaniline - incoordination
- ORAL ALD/LD50 1,1-dimethyl-3-phenylurea - weakness in hindquarters
- ORAL ALD/subacute 3-(p-methoxyphenyl)-1,1-dimethylurea - incoordination/paralysis
- ORAL ALD/subacute 3,4-dichlorophenylurea - incoordination
- ORAL ALD/subacute 3,4-dichloroaniline - cyanosis/methemoglobinemia
- 1-(3,4-dichlorophenyl)-1,3,3-trimethylurea - nothing to report
- Subacute 1-(3,4-dichlorophenyl)-3-methylurea - incoordination/blood destruction
- ALD subacute 3-(3,4-dichlorophenyl)1,1-diethylurea - blood destruction/cyanosis
- 3-(3,4-dichlorophenyl)-1-methyl-1-isopropylurea - nothing to report;
- 3-(3,4-dichlorophenyl)1-methyl-1-sec-butylurea - nothing to report

#12372A

LOW

Acute Oral Toxicity

3-(p-chlorophenyl)-1,1-dimethylurea
3-(o-Chlorophenyl)-1,1-dimethylurea
3-(m-Chlorophenyl)-1,1-dimethylurea
Tetramethylurea
p-Chlorophenylurea
1,1-Dimethyl-3-phenylurea
3-(p-Methoxyphenyl)-1,1-dimethylurea
3-(3,4-Dichlorophenyl)-1,1-dimethylurea
3,4-Dichloroaniline
3,4-Dichlorophenylurea
1-(3,4-Dichlorophenyl)-1,3,3-trimethylurea
1-(3,4-Dichlorophenyl)-3-methylurea
3-(3,4-Dichlorophenyl)-1,1-diethylurea
3-(3,4-Dichlorophenyl)-1-isopropyl-1-methylurea
3-(3,4-Dichlorophenyl)-1-sec-butyl-1-methylurea

Subacute Dietary Toxicity

3-(p-chlorophenyl)-1,1-dimethylurea
1,1-Dimethyl-3-phenylurea

medium

Acute Dermal Toxicity

3-(p-chlorophenyl)-1,1-dimethylurea

Dermal Irritation

3-(p-chlorophenyl)-1,1-dimethylurea
3-(o-Chlorophenyl)-1,1-dimethylurea
3-(m-Chlorophenyl)-1,1-dimethylurea
p-Chlorophenylurea
p-Chloroaniline
1,1-Dimethyl-3-phenylurea
3-(p-Methoxyphenyl)-1,1-dimethylurea
3-(3,4-Dichlorophenyl)-1,1-dimethylurea
3,4-Dichloroaniline

Dermal Sensitization

3-(p-chlorophenyl)-1,1-dimethylurea
3-(o-Chlorophenyl)-1,1-dimethylurea
3-(m-Chlorophenyl)-1,1-dimethylurea
Tetramethylurea
p-Chlorophenylurea
p-Chloroaniline
1,1-Dimethyl-3-phenylurea
3-(p-Methoxyphenyl)-1,1-dimethylurea
3-(3,4-Dichlorophenyl)-1,1-dimethylurea

Subacute Oral Toxicity

Tetramethylurea
p-Chlorophenylurea
3-(p-Methoxyphenyl)-1,1-dimethylurea
3-(3,4-Dichlorophenyl)-1,1-dimethylurea
3,4-Dichloroaniline
3,4-Dichlorophenylurea
1-(3,4-Dichlorophenyl)-1,3,3-trimethylurea
3-(3,4-Dichlorophenyl)-1,1-diethylurea

MEDIUM

Subacute Oral Toxicity

3-(p-chlorophenyl)-1,1-dimethylurea
3-(o-Chlorophenyl)-1,1-dimethylurea
3-(m-Chlorophenyl)-1,1-dimethylurea
p-Chloroaniline
1,1-Dimethyl-3-phenylurea
1-(3,4-Dichlorophenyl)-3-methylurea

Dermal Irritation

Tetramethylurea
3,4-Dichlorophenylurea

Acute Oral Toxicity

p-Chloroaniline

Dermal Sensitization

3,4-Dichloroaniline
3,4-Dichlorophenylurea

12372A

3-(p-chlorophenyl)-1,1-dimethylurea

L

Subacute oral toxicity is of low concern. Rats were exposed to 500 mg/kg for 5 days/week for 2 weeks. There were no deaths. Clinical signs included weakness, cyanosis and weight loss, and autopsy revealed spleen abnormalities. In a second study, 6/6 deaths in rats exposed to 1500 mg/kg 5 days/week for 8 treatments. Clinical signs included discomfort and weakness; autopsy revealed abnormalities of the lungs, liver, kidneys and spleen.

L

Acute oral toxicity is of low concern based on a calculated LD₅₀ of 3600 mg/kg in rats, 670 mg/kg in guinea pigs, and 1500 mg/kg in rabbits. In rats, signs of toxicity included weakness, cyanosis and hind leg paralysis at sublethal doses, and labored respiration, marked weakness and unconsciousness at the higher doses. Abnormalities of the spleen, lungs, liver and kidneys were observed at autopsy. In guinea pigs, signs of toxicity included weakness and weight loss at sublethal doses, and weakness and paralysis with slow respiration at lethal doses. In rabbits, signs of toxicity included weakness at doses of 670 and 1000 mg/kg. No clinical signs were observed at doses of 200 and 450 mg/kg.

EM
medium
Subacute dietary toxicity is of *low* concern based on no deaths in rats (5/sex/dose) exposed to 0.5, 0.05 and 0.005% in the diet for 6 weeks (equivalent to 250, 25 and 2.5 mg/kg/day, respectively). Methemoglobinemia and/or compensatory red blood cell formation was observed at all doses; at 2.5 mg/kg/day, rats were pale and cyanotic with evidence of degenerated cells in the blood.

L

Acute dermal toxicity is of low concern based on no deaths (0/1) in a male rabbit exposed to 2250 mg/kg.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

3-(o-Chlorophenyl)-1,1-dimethylurea

M

Subacute oral toxicity is of medium concern based on lethality in rats exposed to 680, 400 and 300 mg/kg, 5 days/week for 2 weeks. Mortality and corresponding doses (mg/kg) were 6/6 (680), 2/6 (400) and 0/6 (300). Clinical signs included paleness, cyanosis and restlessness and incoordination (300). Autopsy revealed hepatitis (all doses), pulmonary edema and congestion and gastritis (≥ 400), and gastric ulceration and atony (680).

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 3400 mg/kg in rats. Clinical signs included paleness, cyanosis, labored respiration and incoordination (≥ 1000 mg/kg); coma preceding death and pulmonary edema and congestion were observed at lethal doses. Liver injury was observed at autopsy at 1500 mg/kg.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

3-(m-Chlorophenyl)-1,1-dimethylurea

M

Subacute oral toxicity is of medium concern based on 1/6 deaths in rats exposed to 500 mg/kg, 5 days/week for 2 weeks. Clinical signs included discomfort, incoordination, weight loss, paleness and cyanosis. Abnormalities were observed in the lungs and spleen.

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 7500 mg/kg in rats. Clinical signs included weakness, paleness and cyanosis. At autopsy, abnormalities were observed in the spleen at sublethal doses, and liver and kidneys in the decedents.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

Tetramethylurea

M

Dermal irritation is of medium concern based on temporary, strong irritation in guinea pigs exposed by topical application and intradermal injection.

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 2250 mg/kg in rats. Discomfort and weakness were observed at sublethal doses; liver pathology was noted at autopsy.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 450 mg/kg, 5 days/week for 2 weeks. Minimal kidney and liver injury were observed at autopsy.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

p-Chlorophenylurea

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 2250 mg/kg in rats. Clinical signs included discomfort, weakness and incoordination. Liver injury was reported at lethal doses.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 450 mg/kg, 5 days/week for 2 weeks. Clinical signs included hind quarters discomfort and weakness, paleness and cyanosis. Increased hematopoiesis and temporary liver damage were reported.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

p-Chloroaniline

M

Acute oral toxicity is of medium concern based on an approximate lethal dose of 200 mg/kg in rats. Clinical signs included paleness, cyanosis and incoordination (all doses), and marked weakness (≥ 80 mg/kg). Hepatitis and methemoglobinemia were observed in the decedents.

M

Subacute oral toxicity is of medium concern based on cyanosis and incoordination observed in rats exposed to 12 treatments of 40 mg/kg over a 17 day period. There were no deaths (0/6). Spleen enlargement and reversible methemoglobinemia were reported.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

1,1-Dimethyl-3-phenylurea

L

Subacute oral toxicity is of low concern based on 2/6 deaths in rats exposed to 1500 mg/kg, 5 days/week for 2 weeks. Clinical signs included weakness and irritability. Gastric atony, liver damage and spleen abnormalities were observed at autopsy.

L

Acute oral toxicity is of low concern based on a calculated LD_{50} of 6400 mg/kg in rats. Signs of toxicity included discomfort and weakness in the hind quarters (all doses), and pallor and cyanosis at the higher doses. Gastritis was observed at autopsy.

L

Subacute dietary toxicity is of low concern based on no deaths, clinical signs of toxicity or pathology observed in rats (5/sex/dose) exposed to 48 mg/kg/day for 6 weeks.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

3-(p-Methoxyphenyl)-1,1-dimethylurea

L

Acute oral toxicity is of low concern based on a calculated LD₅₀ of 1750 mg/kg in rats. The decedents exhibited gastritis, hepatitis and nephritis. In a second study, rats demonstrated clinical signs including weakness (all doses), incoordination (sublethal doses), and paralysis of the hind quarters (lethal doses). Pulmonary edema and congestion were observed in the decedents.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 300 mg/kg, 5 days/week for 2 weeks. Some evidence of kidney damage was reported.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

3-(3,4-Dichlorophenyl)-1,1-dimethylurea

L

Acute oral toxicity is of low concern based on a calculated LD₅₀ of 3400 mg/kg in rats. Clinical signs included discomfort, weakness, labored respiration and cyanosis. Blood destruction and methemoglobinemia were reported. In a second study, rats demonstrated incoordination, and lung and spleen abnormalities.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 1000 mg/kg, 5 days/week for 2 weeks. Spleen and bone marrow abnormalities were reported.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

L

Dermal sensitization is of low concern based on no allergic skin reactions in guinea pigs.

3,4-Dichloroaniline

M

Dermal sensitization is of medium concern based on allergic skin reactions in guinea pigs (incidence and severity not reported).

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 670 mg/kg in rats. Weakness and cyanosis were observed at the higher doses. Methemoglobinemia and spleen enlargement were reported.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 134 mg/kg, 5 days/week for 2 weeks. Weakness and slight cyanosis were observed. Spleen abnormalities and reversible methemoglobinemia were also reported.

L

Dermal irritation is of low concern based on no irritation in guinea pigs.

3,4-Dichlorophenylurea

M

Dermal irritation is of medium concern based on moderate irritation in guinea pigs.

M

Dermal sensitization is of medium concern based on positive reactions in guinea pigs.

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 1000 mg/kg in rats. Clinical signs included weakness, incoordination and unconsciousness. Liver and/or kidney damage was observed in the decedents.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 200 mg/kg, 5 days/week for 2 weeks. Clinical signs included weakness and incoordination; liver and kidney damage was observed at autopsy.

1-(3,4-Dichlorophenyl)-1,3,3-trimethylurea

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 1500 mg/kg in rats. Clinical signs included marked weakness and breathing abnormalities at the lethal doses. There were no signs at doses <1000 mg/kg.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 10 doses of 300 mg/kg.

1-(3,4-Dichlorophenyl)-3-methylurea

A m

medium
Subacute oral toxicity is of ~~low~~ concern based on 3/6 deaths in rats exposed to 680 mg/kg, 5 days/week for 2 weeks. Clinical signs included marked cyanosis, incoordination, weakness and nervousness. Gastritis, liver damage and spleen abnormalities were observed in the decedents.

L

Acute oral toxicity is of low concern based on a calculated LD₅₀ of 1600 mg/kg in rats. In a second study, rats demonstrated weakness and discomfort at doses of 1000-7500 mg/kg. Lethal doses caused unconsciousness.

3-(3,4-Dichlorophenyl)-1,1-diethylurea

L

Acute oral toxicity is of low concern based on an approximate lethal dose of 5000 mg/kg in rats. Clinical signs included marked discomfort and weakness (>1500 mg/kg). Gastroenteritis was observed in the decedents.

L

Subacute oral toxicity is of low concern based on no deaths (0/6) in rats exposed to 1000

mg/kg, 5 days/week for 2 weeks. Weakness and cyanosis, and compensatory erythropoiesis were reported.

3-(3,4-Dichlorophenyl)-1-isopropyl-1-methylurea

L

Acute oral toxicity is of low concern based on an approximate lethal dose >7500 mg/kg in rats.

3-(3,4-Dichlorophenyl)-1-sec-butyl-1-methylurea

L

Acute oral toxicity is of low concern based on an approximate lethal dose >11000 mg/kg in rats.