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**E. I. DU PONT DE NEMOURS & COMPANY**

INCORPORATED

WILMINGTON, DELAWARE 19898

LEGAL DEPARTMENT

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August 10, 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

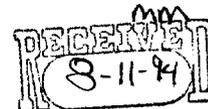
On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA 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.

For Regulatee,

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Counsel  
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8EHQ-92-12179  
INIT

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## 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 standard<sup>2</sup>. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.<sup>3</sup> 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).

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 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.

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<sup>2</sup>In 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".

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

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

- even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent<sup>4</sup>, 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).
- 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.
- 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.<sup>5</sup>
- 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.
- 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.

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.

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<sup>4</sup>The '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.

<sup>5</sup> 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.

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.

## APPENDIX

*Comparison:* Criteria 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>TOXICITY TEST TYPE</u>	<u>1978 POLICY CRITERIA EXIST?</u>	<u>New 1991 GUIDE CRITERIA EXIST?</u>
<b>ACUTE LETHALITY</b>		
Oral	N)	Y}
Dermal	N)	Y}
Inhalation (Vapors)	} <sup>1</sup>	} <sup>2</sup>
aerosol	N)	Y)
dusts/ particles	N)	Y)
<b>SKIN IRRITATION</b>	N	Y <sup>3</sup>
<b>SKIN SENSITIZATION</b>	N	Y <sup>4</sup>
<b>EYE IRRITATION</b>	N	Y <sup>5</sup>
<b>SUBCHRONIC (ORAL/DERMAL/INHALATION)</b>	N	Y <sup>6</sup>
<b>REPRODUCTION STUDY</b>	N	Y <sup>7</sup>
<b>DEVELOPMENTAL TOX</b>	Y <sup>8</sup>	Y <sup>9</sup>

<sup>1</sup>43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporting of specified 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 tot he Agency and if the information meets the criteria set forth in Parts V and VII."

<sup>2</sup>Guide at pp.22, 29-31.

<sup>3</sup>Guide at pp-34-36.

<sup>4</sup>Guide at pp-34-36.

<sup>5</sup>Guide at pp-34-36.

<sup>6</sup>Guide at pp-22; 36-37.

<sup>7</sup>Guide at pp-22

<sup>8</sup>43 Fed Reg at 11112

Only .the term "Birth Defects" is listed.

NEUROTOXICITY	N	Y <sup>10</sup>
CARCINOGENICITY	Y <sup>11</sup>	Y <sup>12</sup>
MUTAGENICITY		
<i>In Vitro</i>	Y <sup>13</sup>	Y <sup>14</sup>
<i>In Vivo</i>	Y)	Y)
ENVIRONMENTAL		
Bioaccumulation	Y)	N
Bioconcentration	Y) <sup>15</sup>	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

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<sup>9</sup>Guide at pp-2122. Includes new detailed criteria regarding statistical treatment, specific observations and the §8(e)-significance of maternal toxicity.

<sup>10</sup>Guide at pp-23; 33-34.

<sup>11</sup>43 Fed Reg at 11112

Only the term "Cancer" listed.

<sup>12</sup>Guide at pp-21. Includes new criteria regarding biological significance and statistical treatment.

<sup>13</sup>43 Fed Reg at 11112; 11115 at Comment 15

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

<sup>14</sup>Guide at pp-23.

<sup>15</sup>43 Fed Reg at 11112; 11115 at Comment 16.

**Attachment 2**

**Study Summary and Report**

CAS #107-13-1

Study Conducted by: Dow Chemical Chem: Acrylonitrile

Title: Teratologic evaluation of acrylonitrile monomer given to rats by  
Gavage

Date 10-22-76

Summary of Effects: Embryotoxicity and fetotoxicity at mid and high dose  
(25 and 65 mg/kg/day)

TERATOLOGIC EVALUATION OF ACRYLONITRILE MONOMER GIVEN  
TO RATS BY GAVAGE

By:

F. J. Murray, K. D. Nitschke, J. A. John, F. A. Smith,  
J. F. Quast, C. D. Blogg, and B. A. Schwetz

Reviewed by:

J. M. Norris and B. A. Schwetz

October 22, 1976

Toxicology Research Laboratory  
Health and Environmental Research  
Dow Chemical U.S.A.  
Midland, Michigan 48640

This study was supported by the companies sponsoring research  
on acrylonitrile and administered by the Manufacturing Chemists  
Association.

## ABSTRACT

This study evaluated the effect of orally administered acrylonitrile on embryonal and fetal development. Pregnant Sprague-Dawley rats were given 0, 10, 25, or 65 mg acrylonitrile/kg/day by gavage on days 6-15 of gestation. Administration of 65 mg acrylonitrile/kg/day, a dose level which caused significant maternal toxicity, produced an increased incidence of fetal malformations; these included acaudia, short-tail, short trunk, missing vertebrae, and right-sided aortic arch. Other signs of embryotoxicity or fetotoxicity seen at this dose level were: increased frequency of early resorption sites detected by sodium sulfide stain, decreased fetal body weight and crown-rump length, and increased incidences of some minor skeletal variants. At 25 mg acrylonitrile/kg/day, less maternal toxicity was noted, but a low incidence of the same anomalies seen at 65 mg/kg/day was observed, suggesting a possible effect on the incidence of malformations at this dose level also. No other evidence of embryotoxicity was noted at 25 mg/kg/day. At the lowest dose level, 10 mg acrylonitrile/kg/day, there was no evidence of toxicity to either the mother or her developing embryo or fetus.

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INTRODUCTION

A study to investigate the effects of maternally ingested acrylonitrile on rat embryonal and fetal development, herein reported, is one of a multi-study toxicological investigation being conducted to evaluate the toxicity of acrylonitrile.

The study was conducted under the auspices of the Manufacturing Chemists Association in the Toxicology Research Laboratory, Health and Environmental Research, The Dow Chemical Company.

MATERIALS AND METHODS

Test Material. The sample of acrylonitrile used for this study was obtained from EI duPont de Nemours and Company, Inc., Industrial Chemicals Department, P.O. Box 27038, Memphis, Tennessee. The sample was identified as having come from tank wagon No. 7363. The purity of the sample was >99%. The specifications of the test material, as provided by EI duPont de Nemours and Company, Inc., were as follows:

Acetone	48 ppm
Acetonitrile	155 ppm
Acidity as HAC	18 ppm
Aldehydes as acetaldehydes	<5 ppm
Color	APHA Clear & Free
Appearance	0
Copper	<0.02 ppm
Distillation range, 760 mm,	76.3-77.5°C
Hydroquinone monomethylether	39 ppm
Iron	<0.02 ppm
Nonvolatile Matter	<10 ppm
Peroxides as H <sub>2</sub> O <sub>2</sub>	<0.02 ppm
pH of 5% aqueous soln.	6.5
Refractive index, sodium D line	25°C 1.3885
Titration value, 0.1N H <sub>2</sub> SO <sub>4</sub>	0.1
Water	0.41%

Animals. Adult Sprague-Dawley female rats (Spartan Research Animals, Haslett, Michigan), weighing approximately 265 grams each, were used in this study. The day on which sperm were found in the vaginal smear was considered day 0 of pregnancy. Animals were housed individually in wire-bottom cages in a room controlled for temperature, humidity, and light cycle. The rats were maintained on food (PURINA LABORATORY CHOW) and tap water free choice.

Experimental Design. A preliminary study was conducted for the purpose of establishing appropriate dose levels for use in the teratologic study, and, hereafter, is referred to as the tolerance study. For the tolerance study, groups of 3-5 bred rats each were given dose levels of 0, 10, 30, 65 or 100 mg acrylonitrile/kg/day by gavage on days 6-15 of gestation.

These rats were necropsied on day 16 of gestation. In the teratologic study, groups of 29-39 bred rats each were given 10, 25 or 65 mg acrylonitrile/kg/day by gavage on days 6-15 of gestation. Acrylonitrile was administered as an aqueous solution; the dose volume was 2 ml/kg of body weight. A group of 43 bred rats was dosed with 2 ml/kg of water alone on the same days of gestation to serve as negative controls. For all animals, the volume of material administered was adjusted daily on the basis of the animal's body weight.

Maternal Observations. Animals were observed daily throughout the gestation period for indications of toxicity from the test material. The body weights of the rats were recorded on days 6, 10 and 16 of gestation. In addition, maternal body weights and the weight of the maternal liver were recorded at the time of cesarean section, day 21. Food and water consumptions were measured at 3-day intervals on days 6-20 of gestation. Because acrylonitrile was noted to cause gastric ulcers in the tolerance study, the stomachs of the bred females were examined grossly at the time of cesarean section for evidence of ulcers and other abnormalities. The stomach of 5-10 rats/dose level were preserved in formalin and saved for histopathologic examination.

Fetal Examination. On day 21 of gestation, the bred rats were sacrificed by carbon dioxide inhalation. The uterine horns were exteriorized through a midline incision in the abdominal wall, and the number and position of live, dead, and resorbed fetuses were noted. The uteri of apparently non-pregnant animals were stained with a 10% solution of sodium sulfide (Kopf et al., 1974) and examined for evidence of early resorption sites; this procedure was conducted solely for the purpose of determining the pregnancy rate, not the rate of resorptions. After being weighed, measured (crown-rump length), and sexed, all fetuses were examined for external alterations and cleft palate. One-third of the fetuses of each litter was examined immediately for evidence of soft tissue alterations by dissection under a low power stereo-microscope (Staples, 1974). All of the pups in each litter were eviscerated and placed in 95% ethanol, cleared and were stained with alizarin red-S (Dawson, 1926) to facilitate examination for skeletal alterations.

Statistical Evaluation. The incidences of pregnancy and maternal death were analyzed statistically by the Fisher exact probability test (Siegel, 1956). The Wilcoxon test as modified by Haseman and Hoel (1974) was used to evaluate the incidence of fetal alterations and resorptions. Maternal and fetal body weights were analyzed statistically by an analysis of variance and Dunnett's test (Steel and Torrie, 1960). In all cases, the level of significance chosen was  $p < 0.05$ .

RESULTS

In the tolerance study, the following signs of toxicity were observed among bred rats given 100 mg acrylonitrile/kg/day by gavage on days 6-15 of gestation: salivation, hyperexcitability, lethargy, convulsions, dyspnea, and upon necropsy, perforating gastric ulcers; three of four rats receiving this dose level died prior to the scheduled necropsy on day 16 of gestation. At 65 mg/kg/day, a decrease in maternal body weight gain was noted during the dosage period, and the non-glandular portion of the stomach was thickened and, in two of four animals, contained small focal areas of erosion and ulceration. Among rats given 30 mg/kg/day of acrylonitrile, a slight thickening of the non-glandular portion of the stomach was observed, but no other signs of toxicity were noted. At 10 mg/kg/day, no adverse effect on the dams was discerned.

In the teratologic study, sialodacryoadenitis, as diagnosed by the presence of swollen salivary glands, was observed in most of the rats in the control and all three experimental groups. Hyperexcitability and salivation were observed in some rats during the period of dosage with 65 mg acrylonitrile/kg/day by gavage on days 6-15 of gestation, but not among those receiving 10 or 25 mg/kg/day. A single death occurred on the first day of dosage among the 29 rats given 65 mg/kg/day of the test material; no maternal deaths were seen at the

lower dose levels or in the control group. Another rat receiving 65 mg acrylonitrile/kg/day delivered her litter on day 20 of gestation, and was observed shortly thereafter to be dyspneic. At necropsy on day 21 of gestation, the nasal turbinates of this animal were occluded by an exudate. The cause-and-effect relationship between the early delivery, the administration of acrylonitrile and the occluded nasal turbinates could not be determined. A thickening of the non-glandular portion of the stomach was seen at the time of cesarean section in most of the dams given 65 mg acrylonitrile/kg/day and in three of those receiving 25 mg/kg/day; this effect was not observed at 10 mg/kg/day.

The body and liver weights of pregnant rats given acrylonitrile by gavage are indicated in Table 1. The mean body weight of the dams receiving 65 mg/kg/day was significantly greater than that of the control dams on day 6 of gestation, i.e., prior to the administration of acrylonitrile. The amount of weight gained by the dams receiving 65 mg/kg/day was significantly decreased on days 6-9 and 10-15 of gestation, the period during which acrylonitrile was given; no effect on body weight gain was observed at the lower dose levels. The maternal liver weight at the time of cesarean section, expressed on the basis of both absolute and relative liver weight, was significantly increased among dams given 65 mg/kg/day, but not among those receiving the lower dose levels.

The food and water consumptions of pregnant rats receiving acrylonitrile by gavage are summarized in Table 2. The amount of food ingested by dams given 25 or 65 mg/kg/day of the test material was significantly less than that of the control dams on days 6-8 of gestation but not during any of the subsequent 3-day intervals measured. At 10 mg/kg/day, no significant effect on food consumption was seen. The amount of water consumed by the dams receiving 65 mg acrylonitrile/kg/day was significantly greater than that of the control dams throughout days 6-20 of gestation. No significant effect on maternal water intake was observed at the lower dose levels.

Observations made at the time of cesarean section are reported in Table 3. The apparent pregnancy rate, i.e., the proportion of bred rats with visible implantation sites at the time of cesarean section was significantly lower among rats given 65 mg acrylonitrile/kg/day than among the control rats. After the uterus of each apparently non-pregnant rat was stained with sodium sulfide, four additional dams with implantation sites, which ranged in number from 12-16, were revealed at the high dose level. No additional pregnancies were detected by sodium sulfide stain among the control, 10 or 25 mg/kg/day groups. When the four pregnancies detected with stain at the high dose level were added to those noted by visual

inspection of the uterus at cesarean section, the total pregnancy rate was not significantly different from that of the control group. Administration of acrylonitrile had no significant effect on the litter size, the fetal sex ratio or the incidence or distribution of resorptions (excluding those detected by sodium sulfide stain). At 65 mg/kg/day, the fetal body weight and crown-rump length were significantly less than the control values; this effect was not observed at the lower dose levels of acrylonitrile.

The incidence of external or soft tissue alterations among litters of rats given acrylonitrile by gavage is indicated in Table 4. The frequency of acaudate fetuses among litters of rats receiving 65 mg acrylonitrile/kg/day was significantly increased compared to the control incidence; a statistically significant increase in the incidence of acaudate and short-tailed fetuses combined was also seen at this dose level. Two acaudate fetuses were noted at 25 mg/kg/day. In the control group, a single short-tailed pup was observed. There were no statistically significant differences in the frequency of either of these tail anomalies alone or combined among litters of rats given the lower dose levels. In all cases of short tail, the length of the tail was less than half the normal length. Of the eight acaudate or short-tailed fetuses observed at 65 mg/kg/day, three

exhibited short trunk and two had an imperforate anus; these abnormalities were not seen in either the control or the other experimental groups.

The soft tissue examination revealed right-sided aortic arch in single fetuses at both 25 and 65 mg/kg/day; in the latter case, this abnormality was seen in an acaudate fetus.

Anteriorly displaced ovaries were seen in single fetuses with tail anomalies at the two higher dose levels. Dilated ureter was seen in single fetuses at both 25 and 65 mg/kg/day; at the highest dose level, this alteration occurred in an acaudate fetus. Dilated renal pelvis was observed in two fetuses of rats receiving 25 mg/kg/day, but was not seen in the other experimental groups or in the control group. In the control and 65 mg/kg/day groups, single fetuses missing a left and right kidney, respectively, were seen; in the latter case, this anomaly occurred in a short-tailed fetus.

The incidence of skeletal alterations among litters of rats given acrylonitrile by gavage is summarized in Table 5. No skeletal alterations occurred among litters of rats given 10 or 25 mg acrylonitrile/kg/day at an incidence significantly different from that of the control litters. In both the control and 25 mg/kg/day groups, a number of fetuses were observed which were missing one thoracic vertebra, one lumbar vertebra and the 13th pair of ribs. At 65 mg/kg/day, a significant increase was seen in the frequency of fetuses

which were missing vertebra(e) other than a single thoracic and a single lumbar vertebra. Each acaudate or short-tailed fetus (and only these fetuses) had this defect which ranged in severity from missing a single lumbar vertebra to missing 11 thoracic, all lumbar and all sacral vertebrae. Also at 65 mg/kg/day, the incidence of fetuses missing more than one pair of ribs was significantly greater than among the control litters; this defect was observed only in fetuses with tail abnormalities and only in those which were also missing thoracic vertebrae. Also noted to occur significantly more often at 65 mg/kg/day were the following alterations: delayed ossification of the 5th sternbrae, split 2nd sternbrae and missing centra of cervical vertebrae. No significant effect on the ossification of the skull bones was observed among litters of rats receiving acrylonitrile at any of the dose levels administered.

#### DISCUSSION

The results of this study demonstrate a potential for acrylonitrile to cause fetal malformations when given to pregnant rats by gavage at high dose levels on days 6-15 of gestation. At 65 mg acrylonitrile/kg/day, fetuses which were missing vertebrae and were either acaudate or short-tailed occurred significantly more often among litters of rats given this dose level than among the control litters. The incidence of acaudate or short-tailed fetuses at the

high dose level was 4% (8/212); the frequency of this defect among the historical control fetuses examined in this laboratory was 0.3% (10/3481), a value consistent with the 0.2% (1/443) incidence seen in the control group of the present study. The actual number of vertebrae missing in each of the affected fetuses at 65 mg/kg/day did not appear to be related to the dose level of acrylonitrile since 4 of the 8 affected fetuses were missing fewer vertebrae than the short-tailed fetus seen in the control group. A number of other anomalies occurred only in acaudate or short-tailed fetuses, including short trunk, anteriorly displaced ovaries, missing ribs, and imperforate anus; each of these abnormalities has been seen in short-tailed or acaudate fetuses from control groups in earlier studies. However, right-sided aortic arch, which occurred in a fetus at 65 mg/kg/day, has never been seen in over 1,000 litters of rats examined in this laboratory prior to this study. Other signs of embryotoxicity evident at 65 mg/kg/day included the following: increased frequency of early resorptions detected by sodium sulfide stain, decreased fetal body weight and crown-rump length, and increased incidences of some minor skeletal variants.

At 25 mg/kg/day, no fetal alteration occurred at an incidence statistically significantly different from that of the control group; however, the same malformations seen at 65

mg/kg/day were also observed at 25 mg/kg/day. The incidence of acaudate fetuses was slightly greater among litters of rats receiving 25 mg/kg/day than among the control litters, and an additional fetus with a right-sided aortic arch was also seen at this dose level. These findings suggest that administration of 25 mg acrylonitrile/kg/day may have caused a slight increase in the incidence of malformations; no other evidence of embryotoxicity was seen at this dose level.

At 10 mg/kg/day, no adverse effect on embryonal or fetal development was discerned.

Signs of maternal toxicity were clearly evident among rats receiving 65 mg acrylonitrile/kg/day, including salivation, hyperexcitability, thickening of the non-glandular portion of the stomach, decreased weight gain, increased liver weight, decreased food consumption, increased water consumption, and one death. The nature and possible significance of acrylonitrile-induced gastric thickening seen in the dam in this study will be the subject of a separate report in which the results of the histologic examination of the stomachs will be given. The only indications of acrylonitrile-induced toxicity among dams receiving 25 mg/kg/day were a slight but statistically significant decrease in food consumption on the first few days of dosage and a thickening of

the non-glandular portion of the stomach in a few rats at the time of cesarean section. No signs of toxicity related to dosage with acrylonitrile were evident at the lowest dose level.

At the higher dose levels, administration of acrylonitrile resulted in toxicity both to the dam and to her developing embryo or fetus, and it is possible that the deleterious effects on the embryo or fetus were directly caused by maternal toxicity. However, it is the authors' opinion that the malformations observed in the present study were not the effect of maternal toxicity alone since, 1) historical data from this laboratory indicate that such malformations have not been seen at an increased incidence among fetuses of pregnant rats stressed to a similar or even greater degree, and 2) there was no apparent correlation between the degree of toxicity seen in the individual dam and the occurrence of fetal malformations. The presence of sialodacryoadenitis, presumably of viral origin, in most of the rats in the control and experimental groups was not believed to significantly affect the outcome of this study since the disease occurred with equal frequency among all groups, and since the control groups in the present study did not appear to be different from past control groups in any respect other than the disease.

In conclusion, administration of acrylonitrile by gavage to rats on days 6-15 of gestation produced malformations and other evidence of embryotoxicity at 65 mg/kg/day, a dose level which caused significant maternal toxicity. At 25 mg acrylonitrile/kg/day, less maternal toxicity was observed, but a low incidence of the same malformations seen at 65 mg/kg/day was noted, suggesting a possible effect on the incidence of malformations at this dose level also. At 10 mg acrylonitrile/kg/day, there was no evidence of toxicity to either the dam or her developing embryo or fetus; no effect on the incidence of fetal alterations was seen at this dose level.

REFERENCES

1. Dawson, A. B. 1926. A note on the staining of the skeleton of cleared specimens with alizarin red-S. Stain Tech. 1, 123-124.
2. Haseman, J. K. and Hoel, D. G. 1974. Tables of Gehan's generalized Wilcoxon test with fixed point censoring. J. Stat. Comp. and Simulation 3, 117-135.
3. Kopf, R., Lorenz, D., and Salewski, E. 1964. Procedure for staining implantation sites of fresh rat uteri. Naunyn-Schmiedebergs Arch. Exp. Path. Pharmacol. 247, 121-135.
4. Siegel, S. 1956. Non-Parametric Statistics for the Behavioral Sciences. McGraw-Hill Book Company, Inc., New York, New York.
5. Staples, R. E. 1974. Detection of visceral alterations in mammalian fetuses. Teratology 9, A-37.
6. Steel, R.G.D. and Torrie, H. H. 1960. Principles and Procedures of Statistics. McGraw-Hill Book Company, Inc., New York, New York.

TABLE 1

BODY AND LIVER WEIGHTS OF PREGNANT RATS RECEIVING ACRYLONITRILE BY GAVAGE

	Dose Level of Acrylonitrile, mg/kg/day <sup>a</sup>			
	0	10	25	65
Number of dams	38	35	29	18
Maternal body weight (g) on gestation				
day 6	259±19 <sup>b</sup>	266±19	256±24	276±19 <sup>c</sup>
10	277±21	283±20	273±22	277±20
16	320±26	325±22	312±25	308±23
21	403±37	401±27	386±42	388±38
Maternal weight gain on gestation				
days 6-9	18±8	17±7	16±10	2±9 <sup>c</sup>
10-15	43±11	42±11	39±12	31±12 <sup>c</sup>
16-20	83±17	76±14	74±24	79±30
Maternal liver weight on gestation day 21				
absolute <sup>d</sup>	15.76±1.88	15.59±1.88	15.76±2.19	17.52±2.16 <sup>c</sup>
relative <sup>e</sup>	39.3±4.4	38.8±4.4	40.9±4.6	45.5±2.7 <sup>c</sup>

<sup>a</sup> Acrylonitrile was given by gavage on days 6-15 of gestation.

<sup>b</sup> Mean ± S.D.

<sup>c</sup> Significantly different from control value by Dunnett's test, p<0.05.

<sup>d</sup> g, mean ± S.D.

<sup>e</sup> g liver/kg body weight, mean ± S.D.

TABLE 2

FOOD AND WATER CONSUMPTION OF PREGNANT RATS RECEIVING ACRYLONITRILE BY GAVAGE

		Dose Level of Acrylonitrile, mg/kg/day <sup>a</sup>			
		0	10	25	65
Food consumed <sup>b</sup> on gestation days	6-8	23±3 <sup>c</sup>	22±2	20±3 <sup>d</sup>	18±3 <sup>d</sup>
	9-11	23±4	24±3	22±3	23±6
	12-14	25±3	26±3	25±4	26±5
	15-17	29±3	28±3	29±4	32±5
	18-20	29±3	29±2	29±4	31±5
Water consumed <sup>b</sup> on gestation days	6-8	46±7	48±6	45±9	66±13 <sup>d</sup>
	9-11	53±8	55±8	56±9	89±24 <sup>d</sup>
	12-14	57±9	58±14	63±9	105±20 <sup>d</sup>
	15-17	67±9	69±9	73±11	103±22 <sup>d</sup>
	18-20	58±18	65±10	67±11	80±23 <sup>d</sup>

<sup>a</sup>Acrylonitrile was given by gavage on days 6-15 of gestation.

<sup>b</sup>Expressed as grams/rat/day.

<sup>c</sup>Mean ± S.D.

<sup>d</sup>Significantly different from control value by Dunnett's test, p<0.05.

TABLE 3

OBSERVATIONS MADE AT THE TIME OF CESAREAN SECTION OF RATS RECEIVING  
ACRYLONITRILE BY GAVAGE

	Dose Level of Acrylonitrile, mg/kg/day <sup>a</sup>			
	0	10	25	65
Number of bred females	43	39	33	29
Number of deaths/no. of females	0/43	0/39	0/33	1/29
Apparent pregnancy rate <sup>b</sup>	88% (38/43)	90% (35/39)	89% (29/33)	69% (20/29) <sup>c,</sup>
Total pregnancy rate <sup>e</sup>	88% (38/43)	90% (35/39)	89% (29/33)	83% (24/29)
Proportion of pregnant animals detected only by sulfide staining <sup>f</sup>	(0/38)	(0/35)	(0/29)	17% (4/24) <sup>d</sup>
Number of litters	38	35	29	18
Implantation sites/dam <sup>g,h</sup>	12±3	12±3	11±4	12±3
Live fetuses/litter <sup>g,h</sup>	12±3	11±3	11±4	12±3
Resorptions/litter <sup>g,h</sup>	0.7±0.9	0.6±0.8	0.4±0.6	0.6±0.7
% Implantations resorbed <sup>h</sup>	6% (26/469)	5% (21/409)	3% (11/323)	4% (10/222)
Litters with resorptions <sup>h</sup>	47% (18/38)	40% (14/35)	34% (10/29)	44% (8/18)
Litters totally resorbed <sup>h</sup>	0	0	0	1
Resorptions/litters with resorptions <sup>h</sup>	1.4(26/18)	1.5(21/14)	1.1(11/10)	1.2(10/8)
Sex ratio, M:F	49:51	49:51	48:52	53:47
Fetal body weight, g <sup>i</sup>	5.68±0.28	5.78±0.25	5.80±0.33	5.26±0.32 <sup>j</sup>
Fetal crown-rump length, mm <sup>i</sup>	44.4±1.0	44.5±1.3	45.0±1.2	43.6±1.2 <sup>j</sup>

<sup>a</sup> Acrylonitrile was given by gavage on days 6-15 of gestation.<sup>b</sup> No. of females with visible implantation sites at the time of cesarean section or necropsy/total no. of bred females.<sup>c</sup> A female which delivered her litter on day 20 of gestation was included in the calculation of the pregnancy rates. The litter was not examined for fetal alterations.<sup>d</sup> Significantly different from control by Fisher's exact probability test,  $p < 0.05$ .<sup>e</sup> No. of females with implantation sites as observed either visually at the time of cesarean section or after staining the uterus with sodium sulfide stain/total no. of bred females.<sup>f</sup> No. of females with implantation sites detected only after staining the uterus with sodium sulfide stain/total no. of females with implantation sites.<sup>g</sup> Mean ± S.D.<sup>h</sup> Data from the four females in which implantation sites were detected only after sodium sulfide staining of the uterus were not included in these calculations.<sup>i</sup> Mean of litter means ± S.D.<sup>j</sup> Significantly different from control mean by Dunnett's test,  $p < 0.05$ .

TABLE 4

## INCIDENCE OF FETAL ALTERATIONS OBSERVED DURING THE EXTERNAL OR SOFT TISSUE EXAMINATION AMONG LITTERS OF RATS RECEIVING ACRYLONITRILE BY GAVAGE

		Dose Level of Acrylonitrile, mg/kg/day <sup>a</sup>			
		0	10	25	65
		No. Fetuses/No. Litters Examined			
EXTERNAL EXAMINATION		443/38	388/35	312/29	212/17
SOFT TISSUE EXAMINATION		154/38	135/35	111/29	71/17
<u>EXTERNAL EXAMINATION</u>		% Affected (No. Affected)			
Acaudate	F <sup>b</sup>	0	0	0.6(2)	2(4) <sup>c</sup>
	L	0	0	7(2)	23(4)
Acaudate or short tail	F	0.2(1)	0	0.6(2)	4(8) <sup>c</sup>
	L	3(1)	0	7(2)	35(6)
Short trunk	F	0	0	0	1(3) <sup>c,d</sup>
	L	0	0	0	18(3)
Imperforate anus	F	0	0	0	1(2) <sup>d</sup>
	L	0	0	0	12(2)
<u>SOFT TISSUE EXAMINATION</u>					
Right-sided aortic arch	F	0	0	1(1)	1(1) <sup>d</sup>
	L	0	0	3(1)	6(1)
Ovaries, anteriorly displaced	F	0	0	1(1) <sup>d</sup>	1(1) <sup>d</sup>
	L	0	0	3(1)	6(1)
Missing kidney, unilateral	F	1(1)	0	0	1(1) <sup>d</sup>
	L	3(1)	0	0	6(1)
Dilated renal pelvis, unilateral	F	0	0	2(2)	0
	L	0	0	7(2)	0
Dilated ureter, left	F	0	0	1(1)	1(1) <sup>d</sup>
	L	0	0	3(1)	6(1)

<sup>a</sup>Acrylonitrile was given by gavage on days 6-15 of gestation.

<sup>b</sup>F = fetuses; L = litters.

<sup>c</sup>Significantly different from control by a modified Wilcoxon test,  $p < 0.05$ .

<sup>d</sup>This alteration occurred only in fetuses with a short or missing tail at this dose level.

TABLE 5

INCIDENCE OF SKELETAL ALTERATIONS AMONG LITTERS OF RATS RECEIVING  
ACRYLONITRILE BY GAVAGE

	Dose Level of Acrylonitrile, mg/kg/day <sup>a</sup>				
	0	10	25	65	
No. Fetuses/No. Litters Examined					
SKELETAL EXAMINATION	443/38	388/35	312/29	212/17	
SKULL BONE EXAMINATION	289/37	253/34	201/24	141/17	
<b>SKELETAL EXAMINATION</b>					
		% Affected (No. Affected)			
Vertebrae - 12 thoracic & 5 lumbar (normal # is 13 T and 6 L)	F <sup>b</sup>	2(7)	0	2(7)	0
	L	3(1)	0	7(2)	0
- missing vertebrae other than 1 thoracic and 1 lumbar <sup>c</sup>	F	0.2(1) <sup>d</sup>	0	0.6(2) <sup>d</sup>	4(8) <sup>d,e</sup>
	L	3(1)	0	7(2)	35(6)
- missing centra of cervical vertebrae (other than C <sub>1</sub> and C <sub>2</sub> )	F	5(23)	8(30)	10(31)	34(71) <sup>e</sup>
	L	29(11)	46(16)	46(13)	88(15)
<b>Ribs</b>					
- missing 13th pair only <sup>f</sup>	F	2(7)	0	2(7)	0
	L	3(1)	0	7(2)	0
- missing more than 1 pair <sup>g</sup>	F	0	0	1(2) <sup>d</sup>	2(4) <sup>d,e</sup>
	L	0	0	7(2)	24(4)
<b>Sternebrae</b>					
- delayed ossification, 5th	F	2(9)	3(13)	4(13)	15(31) <sup>e</sup>
	L	16(6)	23(8)	34(10)	59(10)
- missing, 5th	F	0	0	1(2)	1(2)
	L	0	0	7(2)	12(2)
- split, 5th	F	1(4)	1(3)	1(3)	4(8)
	L	10(4)	9(3)	10(3)	30(5)
- split, 2nd	F	0	0	0	2(4) <sup>e</sup>
	L	0	0	0	24(4)
<b>SKULL BONE EXAMINATION</b>					
- delayed ossification, any skull bone	F	7(21)	6(15)	6(12)	4(5)
	L	30(11)	26(9)	29(7)	18(3)

<sup>a</sup>Acrylonitrile was given by gavage on days 6-15 of gestation.

<sup>b</sup>F = fetuses; L = litters.

<sup>c</sup>The actual number of thoracic, lumbar and sacral vertebrae of each of the affected fetuses were as follows (normal # is 13 T, 6 L, 4 S): Control - 12T, 2L, 0S; 25 mg/kg/day - 2T, 0L, 0S, 2T, 1L, 1S; 65 mg/kg/day - 13T, 3L, 0S; 3T, 0L, 0S; 13T, 6L, 2S; 7T, 3L, 0S; 13T, 3L, 0S; 2T, 0L, 0S; 3T, 0L, 0S; 13T, 5L, 4S.

<sup>d</sup>This alteration occurred only among fetuses with short or missing tail at this dose level.

<sup>e</sup>Significantly different from control by a modified Wilcoxon test, p<0.05.

<sup>f</sup>This alteration occurred only among fetuses with 12 thoracic and 5 lumbar vertebrae.

<sup>g</sup>The affected fetuses exhibited 0-7 pairs of ribs (normal # is 13).



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107-13-1

INFORMATION TYPE:	P	F	C	INFORMATION TYPE:	P	F	C	INFORMATION TYPE:	P	F	C
0201 ONCO (HUMAN)	01	02	04	0216 EPI/CLIN	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 CELL TRANS (IN VITRO)	01	02	04	0218 HUMAN EXPOS (ACCIDENTAL)	01	02	04	<u>0243</u> CHEM/PHYS 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 ECO/AQUA TOX	01	02	04	0245 CLASTO (ANIMAL)	01	02	04
0206 REPRO/TERATO (HUMAN)	01	02	04	0221 ENV. OCC/REL/FATE	01	02	04	0246 CLASTO (HUMAN)	01	02	04
<u>0207</u> 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 REQUEST DELAY	01	02	04	0248 PROD/USE/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	0299 OTHER	01	02	04
0211 CHR. TOX. (HUMAN)	01	02	04	0226 CONFIDENTIAL	01	02	04				
0212 ACUTE TOX. (ANIMAL)	01	02	04	0227 ALLERG (HUMAN)	01	02	04				
0213 SUB ACUTE TOX (ANIMAL)	01	02	04	0228 ALLERG (ANIMAL)	01	02	04				
0214 SUB CHRONIC TOX (ANIMAL)	01	02	04	0239 METAB/PHARMACO (ANIMAL)	01	02	04				
0215 CHRONIC TOX (ANIMAL)	01	02	04	0240 METAB/PHARMACO (HUMAN)	01	02	04				

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
<u>YES</u>	YES (DROP/REFER)	RAT	LOW			
CAS SR	NO	NO (CONTINUE)	<u>MED</u>	HIGH		
DETERMINE	REFER:					

COMMENTS: Develop, juvenile  
65 mg/kg - 1 dam died by periclitale, dec wt gain, food consumption, inc liver, but inc incidence of fetal malformations - acroder, short tail, short trunk, missing vertebrae, right-sided eye, arch, inc freq of fetal resorptions, dec fetal wt, inc incidence of skeletal variations  
10 mg/kg - NOAEL  
25 mg/kg - less severe maternal toxicity, low incidence of malformations