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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 6/28/91CAP 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,

8EHQ-92-11663
INIT 10/27/92

88920009934

Mark H. Christman
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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[2]. 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).

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[2]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".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a 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 criteri. 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 intent[4], 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.
- othe "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];
- othe "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.
- othe "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 .

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[4]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.

[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 con.munity 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 Environemntal 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.*

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
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]

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[6]43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporitng of specifiec effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemicalL 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."

[7]Guide at pp.22, 29-31.

[8]Guide at pp-34-36.

[9]Guide at pp-34-36.

[10]Guide at pp-34-36.

[11]Guide at pp-22; 36-37.

[12]Guide at pp-22

[13]43 Fed Reg at 11112

"Birth Defects" listed.

[14]Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	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
Reprodcutive	N	N

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[15] Guide at pp-23; 33-34.

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed: *in vivo* vs *invitro* discussed: discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112; 11115 at Comment 16.

CAS # 920-66-1
Chem: Hexafluoroisopropanol (HFIP)
Title: Primary Irritation and Local anesthetic activity
Date: 1/11/65
Summary of Effects: Corneal opacity; testes affected

File. Hexafluoroisopropanol MR-584 Haskell Laboratory File

cc: D. G. Pye (4) - 328/302 Experimental Station
C. L. Robbs - Jackson Laboratory
R. D. Richardson - Jackson Laboratory
W. T. Robinson - Jackson Laboratory
J. R. Williamson, Jr. - Process, Kinston (2)

E. I. du Pont de Nemours and Company
Haskell Laboratory for Toxicology and Industrial Medicine

HASKELL LABORATORY REPORT NO. 2-65 MR NO. 584

Material Tested: Hexafluoroisopropanol (HFIP) Haskell No.: 2856

Material Submitted by: C. L. King, Central Research Department Other Codes: A-279-168

References: 1) Haskell Laboratory Report No. 46-62: Inhalation Toxicity of Hexafluoroacetone (HFA), HFA·1 1/2 H_2O and HFA·9 H_2O
2) Haskell Laboratory Report No. 47-62: Inhalation Toxicity of HFA·2 H_2O

PRIMARY IRRITATION AND LOCAL ANESTHETIC ACTIVITY

Procedure: The compound was tested on one male albino guinea pig. The entire back of the guinea pig was closely shaved from neck to pelvis and the area was pricked lightly with a sharp pointed probe to establish the area of maximum sensitivity. Four circular areas, 2.1 cm in diameter were marked out on the back of the animal near the mid-line (the most sensitive area). One drop of undiluted and of 10%, 1% and 0.1% wt/vol dilution in water was applied severally to the four areas. The area was tested by pricking with the probe at frequent intervals after application.

The undiluted material produced erythema at the site of contact; none of the dilutions produced primary skin irritation. No anesthetic effect on the skin was produced at any concentr[illegible].

INHALATION TOXICITY

Procedure: The liquid HFIP was metered at a known constant rate into a T-tube where it was vaporized and diluted with a constant known flow of dried air. The vapor-laden stream was then fed into an exposure chamber containing four male ChR-CD rats per exposure. Initial body weight of the rats was 259-295 grams.

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Results:

Concentration HFIP (nominal ppm)	Exposure Time (hrs.)	Mortality Ratio	Fate
6400	1:20	4/4	All dead by 80 min. after start of exposure
3200	3:20	4/4	All dead by 200 min. after start of exposure
1600	4:00	0/4	Sacrificed 11 days postexposure
800	4:00	0/4	Sacrificed 9 days postexposure
200	4:00	0/4	Sacrificed 10 days postexposure

Clinical Observations: At 6400 and 3200 ppm, lacrimation, salivation, nasal drainage, gasping, and corneal opacity were observed. Unconsciousness occurred at 10-60 minutes after the start of these two exposures and deaths occurred 45-60 minutes later. At sublethal concentrations, corneal opacity, gasping and nasal drainage were not observed. Unconsciousness also occurred at the 1600 ppm level; persisting for 1-3 hours after the end of the exposure. Lacrimation occurred at 1600 and 800 ppm, but not at 200 ppm.

Pathology: Gross examination showed brain change at all levels which appeared to be dose-related. The spleen, lungs, and livers were also affected in at least a few of the animals at all levels. At sublethal levels, liver and kidney weights were about 20% below normal and testicular weight about 10% below normal at sacrifice.

Histologically, testicular effect manifested as oligospermia and interstitial fibroplasia was observed at all exposure levels, as was brain neuronal damage, hypoplasia of the thymus medulla, and increased mitotic activity in the liver. The brain and liver changes appeared to be dose related, while the thymus and testicular changes were similar in magnitude at all dose levels where they occurred. Histological examination of surviving rats also indicated that the pancreatic, stomach, duodenal, and lung changes also observed at lethal levels were probably transitory and dose-related in magnitude. Aberrations were also observed histologically in the bone marrow and spleen of rats 9-11 days after exposure to 1600 and 800 ppm of HFIP, indicating an effect on the hemopoietic system. These effects also appeared to be dose-related and were not observed at the lowest exposure level.

Discussion & Recommendations: The ALC of 1600-3200 ppm for hexafluoroisopropanol would appear to indicate a low order of acute lethality. However, this number, taken by itself, does not give a complete picture of the toxicity of this compound. The major hazard from HFIP appears to arise from organ changes which may be persistent or permanent in nature. Some of these changes were initiated at even the lowest atmospheric level tested.

In view of the known skin penetration of isopropanol and the absence of any skin absorption toxicity information for HFIP, extra care should be used in handling this compound, even in an adequate hood.

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HFIP and the hexafluoroacetones already tested (see References 1 and 2) all seem to affect the testes. The difference appears to be merely one of degree. Both classes of compounds also caused corneal opacity.

The inhalation tests reported here indicate that the toxicology of hexafluoroisopropanol will be similar to that observed for the hexafluoroacetones and it should be handled with the same care used for these latter compounds (i). The tests to date on HFIP do not permit setting a safe atmospheric level for working areas.

If extensive use of hexafluoroisopropanol is contemplated, the following additional tests are recommended:

1. Subacute inhalation (with atmospheric analysis and critical reexamination of the testicular effect reported here)
2. Skin absorption acute toxicity
3. Eye tests similar to those used for the hexafluoroacetones

Summary: The ALC of hexafluoroisopropanol for rats has been determined as 1600-3200 ppm for a four-hour exposure. However, widespread organ damage was observed at this level. Heart, lung, liver, brain, pancreas, gastrointestinal, testicular and thymus changes were still evident microscopically ten days after exposure at even a nominal 200 ppm. Further toxicological testing is recommended if additional work is contemplated with this compound.

(i) This would not be surprising, since isopropanol is known to be converted to acetone in humans. A first assumption would be that the fluorinated analogs would be at least partially metabolized by the same routes.

Report by: JANE K. WIER

S. D. MORRISON

Richard S. White

Approved by: J. Wesley Clayton Jr

JKW/SDM/RSW/mfs
Date: January 11, 1965