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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 process issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

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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 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*.

| TEST TYPE | 1978 POLICY CRITERIA EXIST? | New 1991 GUIDE CRITERIA EXIST? |
|--|--|---|
| ACUTE LETHALITY | | |
| Oral | N ⁶ | Y ⁷ |
| Dermal | N ⁶ | Y ⁷ |
| Inhalation (Vapors) | Y ⁶ | Y ⁷ |
| aerosol | N ⁶ | Y ⁷ |
| dusts particles | N ⁶ | Y ⁷ |
| 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 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 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.

CAS# 920-66-1

Chem: 2H-Hexafluoro-2-propanol (hexafluoroisopropanol;
HFIP)

Title: Acute inhalation toxicity

Date: 3/28/68

Summary of Effects: unconsciousness; loss of righting reflex

Copies to: C. W. Maynard, Jr. (6)
 R. D. Richardson (1)
 W. D. Cruz (Parlin) (1)

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

HASKELL LABORATORY REPORT NO. 66-68 MR NO. 894
 Material Tested: 2H-Hexafluoro-2-propanol (Hexafluoroisopropanol;
 HFIP)

Haskell No.: 4848

Material Submitted by: C. W. Maynard, Jr., Organic Chemicals Department
 Jackson Laboratory Other Codes: FPS-1318

ACUTE INHALATION TOXICITY

Introduction: Previous work at Haskell Laboratory (1) indicated that hexafluoroisopropanol had an Approximate Lethal Concentration (ALC) of 1600-3200 ppm (v/v) based on the nominal concentration for a four-hour inhalation exposure with rats. It was also reported that widespread organ damage occurred at nominal levels as low as 200 ppm. Subsequently, rats exposed to an average analytical level of 300 ppm (2) for ten four-hour exposures, using a newer sample of HFIP, did not reveal any organ damage attributable to the compound. In order to resolve the question of organ damage reported at acute exposure levels, the Organic Chemicals Department requested that we conduct another determination of the acute inhalation toxicity of HFIP, using a recent production sample.

Procedure: The test material was metered by means of a syringe drive into a glass T-tube heated at 95-120°C to insure complete vaporization. The resulting vapor was carried by a measured air stream into a sixteen-liter exposure chamber containing six CHR-CD male rats of 249-250 grams initial body weight per exposure. All exposures, except one, were for four hours. During each exposure, the chamber atmosphere was analyzed 2 to 4 times per hour by a gas chromatographic method. For pathologic examination, two rats dying during an exposure; two rats surviving 14 days after an exposure where rats died; and two rats at each of 1, 3 and 7 days after exposure to a nonlethal dose were sacrificed.

Results:

| Analytical Concentration mg/L | % Saturation @ 25°C (3) | Mortality Ratio | During Exposure | Post-Exposure |
|--|-------------------------|-----------------|--|---|
| 21.2 | 1.46 | 6/6 | Lethal Levels: Face-pawing, lacrimation, salivation, irregular breathing, gasping, hyperemia, incoordination, unresponsiveness, unconsciousness and death. Onset, severity and duration of all of these signs were dose related. | Lethal Levels: Unconsciousness, loss of righting reflex, labored breathing, hyperemia, pupillary dilation with accommodation. Duration and severity of these signs were dose related. |
| 17.0 | 1.17 | 5/6 | | |
| 13.7 | 0.94 | 4/6 | | |
| 13.2 | 0.91 | 2/6 | | |
| 12.2 | 0.84 | 0/6 | | |
| 8.3 | 0.57 | 0/6 | | |
| LC ₅₀ = 1974 ppm (v/v) or 13.5 mg/L (4) | | | | |
| 95% Confidence Limit = 1778 ppm (12.2 mg/L) - 2152 ppm (14.2 mg/L) | | | | |

Clinical Signs

| Immediate | 1-14 Days |
|--|---|
| Lethal Levels: Face-pawing, lacrimation, salivation, irregular breathing, gasping, hyperemia, incoordination, unresponsiveness, unconsciousness and death. Onset, severity and duration of all of these signs were dose related. | Lethal Levels: Unconsciousness, loss of righting reflex, labored breathing, hyperemia, pupillary dilation with accommodation. Duration and severity of these signs were dose related. |

Results (Cont'd.):

| Analytical Concentration mg/L ppm (v/v) | % Saturation @ 25°C (3) | Mortality Ratio | Clinical Signs | |
|--|-------------------------|-----------------|--|---|
| | | | During Exposure | Post-Exposure Immediate 1-14 Days |
| | | | opacity appeared in all succumbing rats immediately after death. Deaths from 1 hour of exposure to 1-1/2 hour post exposure. | |

Nonlethal Levels: Same as lethal Nonlethal Levels: Same as Same as lethal levels except no deaths. Onset, lethal levels except no severity and duration of signs pupillary dilation. dose related.

Pathology: The two rats autopsied after dying during an exposure (3085ppm) both showed reddish areas in the lungs. No other gross abnormalities which could be attributed to the compound were observed in these rats or in any other rats autopsied. Kidney, liver, trachea, lung, brain, testes, bone marrow, spleen, thymus and gastrointestinal tract tissues were examined microscopically. The only effect observed that was suggestive of a test material effect was brain neurone damage. This was observed only in the two rats that were autopsied after dying during exposure to 3085 ppm of HFIP. None of the other tissue effects reported in rats exposed acutely to an earlier sample of HFIP (H-2856) by inhalation (1) were observed. This is in agreement with the previously reported histopathologic findings for a subacute inhalation test with HFIP (H-4165; Ref.2). However, as with H-2856 and H-4165, no histopathologic effects were observed in lung tissues, although the clinical signs indicated that the material was a respiratory irritant.

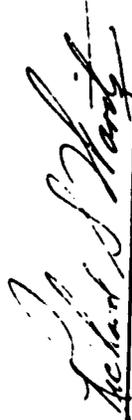
Discussion: No explanation is apparent at this time for the disparity in histopathologic effects observed in rats after acute inhalation exposure to two different samples of HFIP at comparable concentrations. The histopathologic effects reported in Ref. 1 are very similar to those reported for hexafluoroacetone (HFA) and its hydrates (5,6; HFIP is prepared from HFA). However, recent concurrent analysis of all 3 samples of HFIP used in the inhalation tests (7) detected only 0.01% HFA in the first sample of HFIP (H-2856). On the basis of the inhalation studies with HFA and its hydrates, this would not be sufficient to cause the histopathologic effects reported for rats inhaling this sample. The disparity could be explained on the basis of HFA content if the first sample of HFIP contained more HFA at the time of testing than at the time of analysis, six years later. No HFA was found in the current sample of HFIP (H-4848) and only 0.003% in the sample used for subacute inhalation testing (H-4165).

Summary and Recommendations: The acute LC₅₀ for 1966 production HFIP based on four-hour rat exposures is 1974 ppm (0.927 atmospheric saturation at 25°C) with 95% C.I. of 1778-2152 ppm. This is not considered to be significantly different from that reported for earlier production material (1). Except for the absence of nasal drainage in the rats in this present test, the clinical signs observed in the present test were essentially the same as those observed in the previous acute test at comparable levels (1). Thus, HFIP must still be considered a respiratory irritant. Brain neurone damage was observed in rats succumbing to an inhalation exposure at 1.46% of the atmospheric saturation concentration at 25°C, also in agreement with the inhalation test results reported previously (1). Other tissue effects, apparently caused by the earlier sample, were not observed with this sample. In view of the inhalation toxicity of HFIP at small fractions of the atmospheric saturation concentration, the severe and progressive eye damage (2) and severe skin irritation (2,3) that it also causes, it is recommended that HFIP be handled only by adequately instructed personnel.

References:

- (1) Haskell Laboratory Report 2-65.
- (2) Haskell Laboratory Report 60-66.
- (3) On basis of vapor pressure of 160 mm Hg @25°C as reported by C. W. Maynard, Jr., Saturation Concentration @25°C is thus 210,465 ppm or 1446.5 mg/L. Ppm is on a volume/volume or moles per million moles basis.
- (4) Statistical analysis by method of J. T. Litchfield, Jr., F. Wilcoxon, J. Pharmacol. and Expt'l. Therap., 96, 99 (1949).
- (5) Haskell Laboratory Report 46-62.
- (6) Haskell Laboratory Report 47-62.
- (7) Letter, R. F. Hein to R. S. Waritz, 9/18/67.
- (8) Haskell Laboratory Report 42-67.

Report by:


Richard S. Waritz
Chief, Inhalation Toxicology Section

Approved by:


John P. Zapp, Jr.
Director

RSW/sjh

Date: March 28, 1968