Hypothesis (and premise) for etiology of vaper's lung (EVALI)

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There is an established link between eosinophilic pneumonia and HFC134a
https://www.ncbi.nlm.nih.gov/pubmed/?term=17827848

The following can be extracted with R134a (solvent/refrigerant/propellent):

1. Cannabinoids (THC/CBD oil)
2. Flavorants (eg limonene, mango, coconut)
3. Oils, vitamins (eg. tocopherols)

Links to sites describing the use of R134 as the solvent to extract cannabinoids:

Extraction Magazine

Several companies sell extractors that use HFC134a (aka R134a) as the solvent

Below is one such company:
http://www.thepure5.com/cannabisIndustry

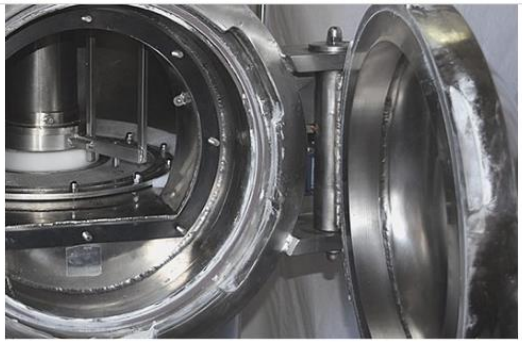
PURE 5™

Why Pure5 Our Devices Login Register

ABOUT PURE 5™

WHO WE ARE

PURE5 TM is the most innovative extraction company. With our superior **Liquefied Gas Extraction** Technology and unique approach to processing material in the field of hemp we have set a new level of extraction standards.



Our Technology

Initially created for food, pharmacy, and perfumery products. Soon after launch, PURE5 TM received overwhelming interest from the hemp industry due to its pure and potent end product, which has turned the company's devices into the best technological ally for hemp oil companies.

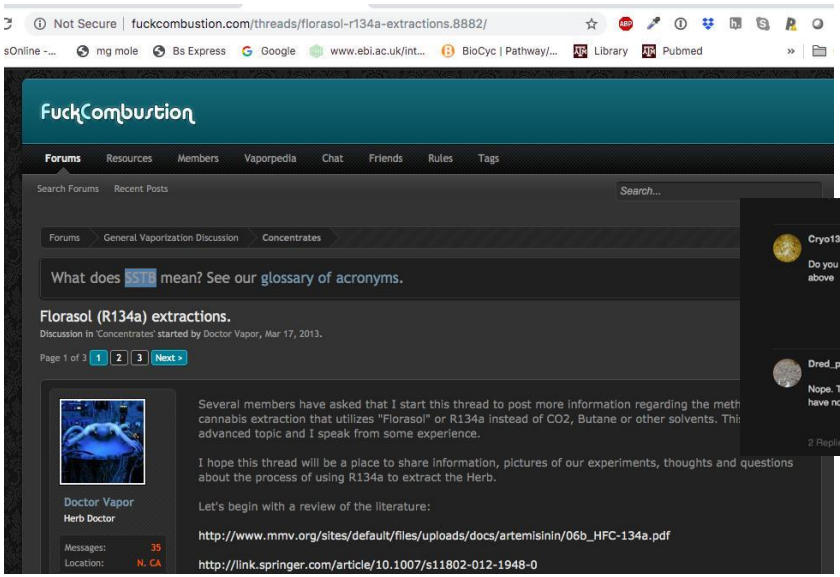
Our Machines

The machine is a game-changer because it uses low temperature and pressure to process the material, takes a fraction of the energy as its CO_2 competitors, and can handle fragile natural ingredients with little degradation.

Our Products

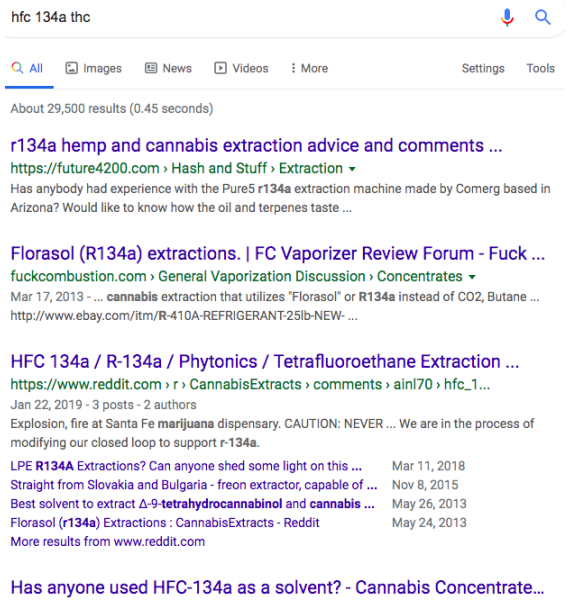
We are so confident in the superiority of the final product that we invite all hemp growers and dispensary owners to compare independent, third-party lab results of Pure5's oils with those created by other extraction technologies.

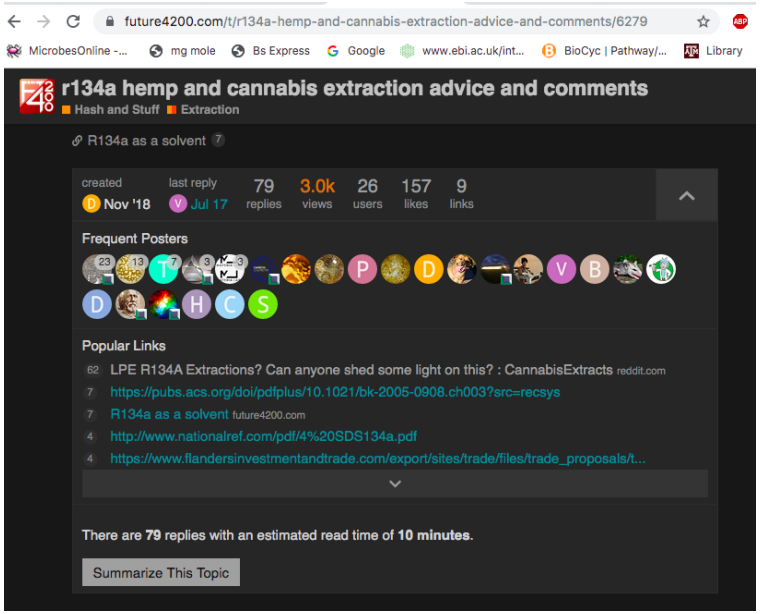
It is also easy to find links to producers explaining how to "do-it-yourself”

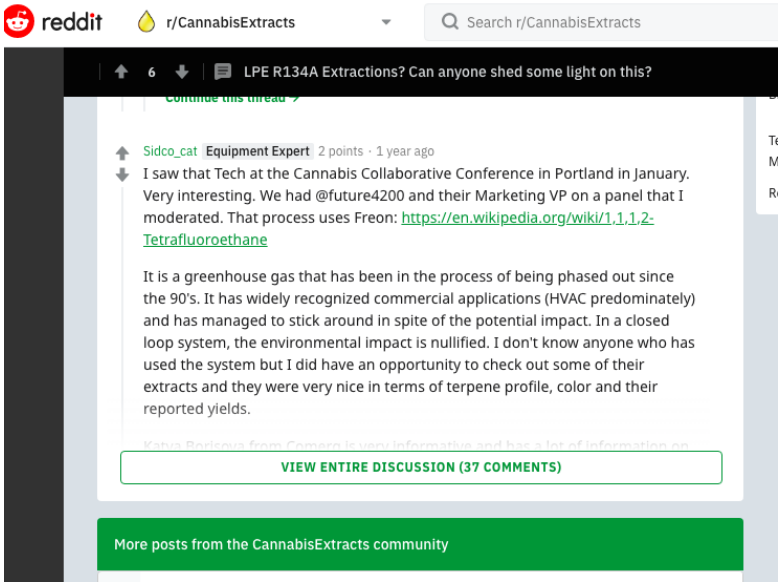


Example links:

[Future4200](#)
[Reddit Cannibis Extraction](#)







The link below reports a case where a woman developed a hypersensitivity to R134a (1,1,1,2-tetrafluoroethane) that resulted in eosinophilic pneumonia.

https://www.ncbi.nlm.nih.gov/pubmed/17827848

Extrinsic Allergic Alveolitis with Eosinophil Infiltration Induced by 1,1,1,2-Tetrafluoroethane (HFC-134a): A Case Report

Takashi Ishiguro[1], Masahide Yasui[1], Yusuke Nakade[2], Hideharu Kimura[1], Nobuyuki Katayama[1], Kazuo Kasahara[1] and Masaki Fujimura[1]

Abstract

A 22-year-old woman was admitted with symptoms of dyspnea and fever with pulmonary infiltrates noted on her chest X-ray study. She developed these symptoms in the workplace; her job included the removal of body hair using a diode-laser with 1,1,1,2-tetrafluoroethane (HFC134a, an alternative to chlorofluorocarbon) as a coolant. A chest X-ray examination revealed ground-glass opacities in the lower lung fields, and a chest computed tomographic study showed diffuse centrilobular opacities. An examination of the bronchoalveolar lavage fluid revealed increased lymphocytes with a slight increase in the number of eosinophils. An examination of the transbronchial biopsy specimens revealed eosinophil infiltration. A peripheral blood eosinophilia was also seen. The patient's symptoms, chest X-ray findings, and arterial blood gas analysis all returned to normal within a week. A challenge test of 1,1,1,2-tetrafluoroethane (HFC134a) inhalation was performed, which resulted in an elevation of body temperature, the development of a cough, and laboratory data indicating increased inflammation. We then determined the patient's diagnosis to be extrinsic allergic alveolits with eosinophil infiltration, caused by HFC134a.

Key words: extrinsic allergic alveolitis, HFC-134a, eosinophilia

There is also a link between development of eosinophilic pneumonia and eosinophilic diseases (such as EPGA) & use of metered dosed inhalers utilizing R134a as a propellant

Example warning on packaging of mdi-administered corticosteroids AND Leukotriene receptor antagonists (this one is from "Flovent")

5.12 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

In one of the original studies demonstrating the safety of R134a as a replacement for CFCs used in mdis (a change required by the Montreal protocol) showed a study participant developing eosinophilia. A link to that study is below.

https://www.ncbi.nlm.nih.gov/pubmed/?term=8832493

J. Pharm. Pharmacol. 1996, 48: 596–600
Received August 4, 1995
Accepted November 23, 1995

Twenty-eight-day Double-blind Safety Study of an HFA-134a Inhalation Aerosol System in Healthy Subjects

LESTER I. HARRISON, DAVID DONNELL*, JEAN L. SIMMONS*, BRUCE P. EKHOLM, KATHERINE M. COOPER AND PETER J. WYLD†

*Pharmacokinetics/Drug Metabolism and Statistical Data Services Departments, 3M Pharmaceuticals, St Paul MN, USA, *Clinical Research Department, 3M Health Care, Ltd, Loughborough, UK, and †Inveresk Clinical Research, Edinburgh, UK*

Abstract

A 28-day double-blind parallel group study has been conducted to compare the safety and tolerability of HFA-134a, a chlorofluorocarbon-free propellant in a pressurized metered-dose inhaler (MDI A), with a chlorofluorocarbon propellant (MDI C).

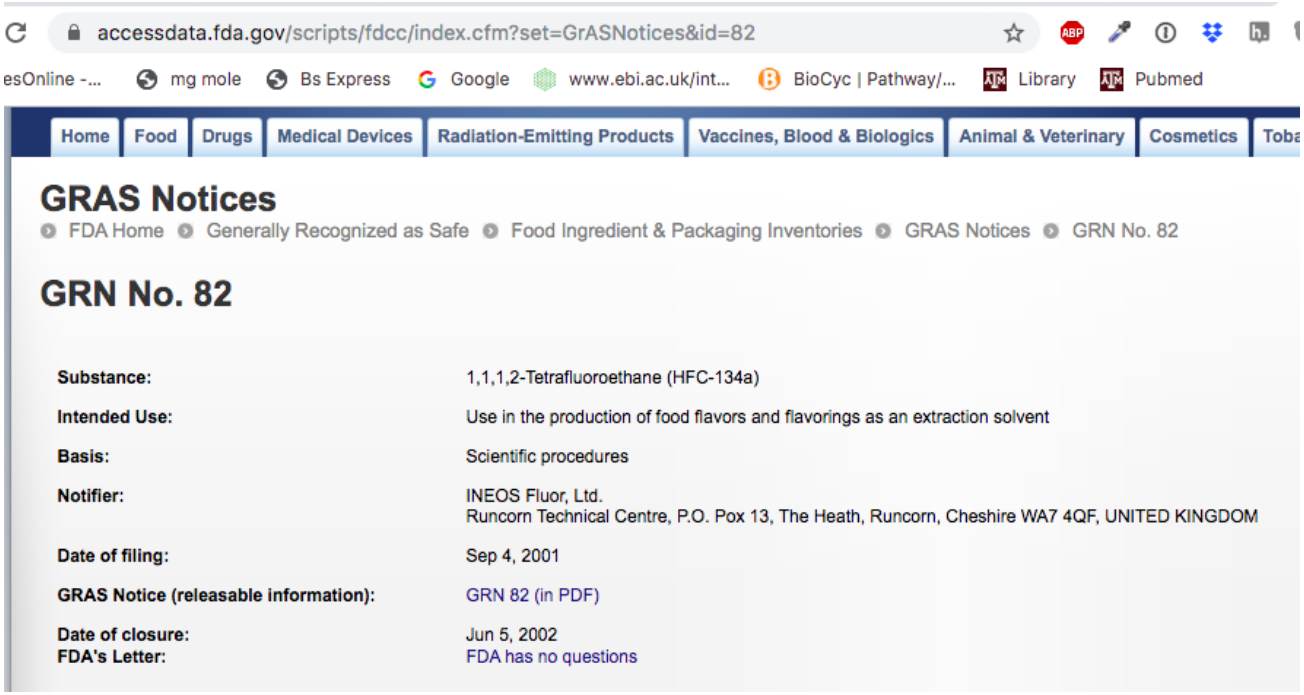
Sixteen subjects were randomly assigned to receive one of the two MDIs, either four inhalations four times per day for 14 days or eight inhalations four times a day for 14 days, and were then crossed over to the alternative exposure regime with the same propellant for the next 14-day period. No clinically significant changes occurred in blood pressure, heart rate, electrocardiograms, pulmonary function (FEV_1, FVC, $FEF_{25-75\%}$), haematology or serum chemistry. One subject in the MDI A group had elevated eosinophil counts throughout the study; there were no other remarkable clinical laboratory data. Fifty six adverse events were related to the study propellants; 34 of these occurred in the MDI C group and 22 in the MDI A group. For each adverse event no statistically significant differences were detected between propellant systems or between exposure levels. The most frequent adverse event was headache, which was reported by four subjects with each propellant system. Blood samples for HFA-134a in the MDI A group were collected on day 28 to measure systemic absorption. Blood levels of HFA-134a were detected in all subjects given this propellant within 1 min post-exposure, and these levels decreased to one-tenth of the original value by 18 min after the start of exposure.

The safety and tolerability of an HFA-134a chlorofluorocarbon-free system was demonstrated over 28 days of exposure in healthy subjects. These negative results are clinically important because they indicate it will be safe to proceed with the study of this chlorofluorocarbon-free system in asthmatic patients.

The FDA granted R134a "Generally Recognized as Safe" (GRAS) status. It's now used as a solvent to extract flavorants used in foods & vaping products

If you are a doctor treating the emerging eosinophlic GI diseases (eg eosinophilic esophagitis), take note

https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=82



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Office of Premarket Approval (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C St SW
Washington, DC 20204

Our Ref.	Direct Line	Ext	Date
fgcr48a1	01928 515081	5081	23 August 2001

Dear Sir/Madam

Subject: Notice of GRAS exemption for 1,1,1,2-tetrafluoroethane (HFC-134a)

Pursuant to the proposed rule outline at 62 Fed. Reg. 18939 (April 17, 1997) INEOS Fluor Ltd. hereby submits notification that the use of 1,1,1,2-tetrafluoroethane (HFC-134a) as an extraction solvent in the production of food flavors and flavorings is exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act because the notifier has determined that such use is generally recognized as safe (GRAS).

https://pubs.acs.org/doi/abs/10.1021/bk-2005-0908.ch003

pubmed eosinophilic esophagitis

year	count
2019	223
2018	320
2017	261
2016	252
2015	260
2014	239
2013	190
2012	164
2011	145
2010	112
2009	114
2008	95
2007	77
2006	67
2005	39
2004	32
2003	21
2002	15
2001	10
2000	10
1999	4
1998	7
1997	6
1996	4
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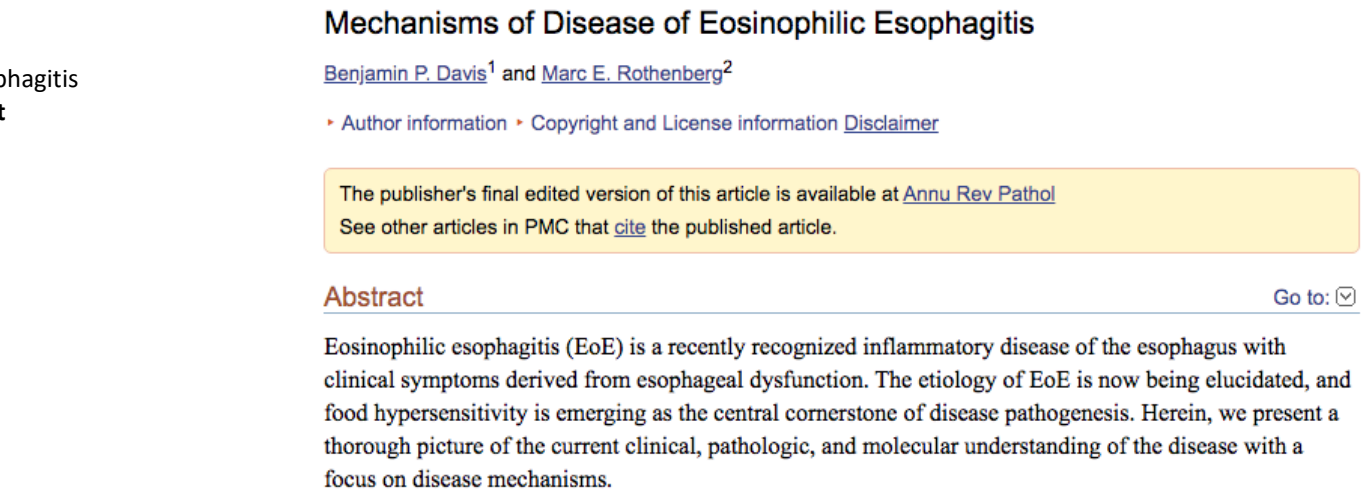
1993	3
1987	1
1985	2
1984	3
1983	1
1982	1
1981	1
1978	1
1976	1



Mechanisms of Disease of Eosinophilic Esophagitis

Benjamin P. Davis[1] and Marc E. Rothenberg[2]

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The publisher's final edited version of this article is available at Annu Rev Pathol
See other articles in PMC that cite the published article.

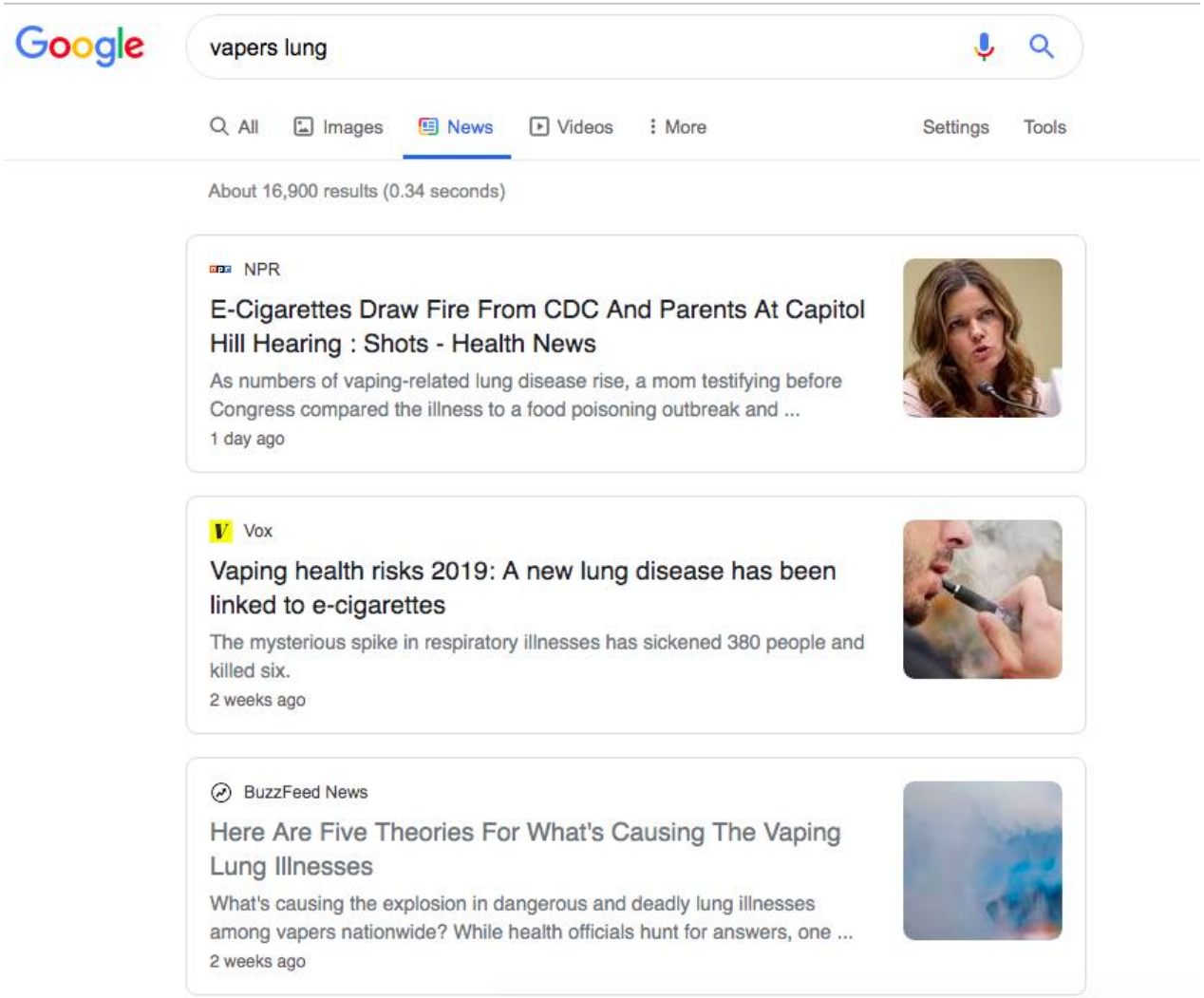
Abstract Go to:

Eosinophilic esophagitis (EoE) is a recently recognized inflammatory disease of the esophagus with clinical symptoms derived from esophageal dysfunction. The etiology of EoE is now being elucidated, and food hypersensitivity is emerging as the central cornerstone of disease pathogenesis. Herein, we present a thorough picture of the current clinical, pathologic, and molecular understanding of the disease with a focus on disease mechanisms.

HFA 134 given GRAS status (deregulation)

The FDA approved HFC 134a as a food-grade item. It is used as a solvent to extract flavors (eg. from vanilla beans) and in some cases for the purification of pharmaceuticals. In 2002, it was granted GRAS status. **One cannot help but think of the sudden increase in incidence of eosinophilic GI diseases during this time frame.** HFC 134a is also used to extract fragrances for perfumes, as the propellant in many aerosols (computer dusters, household cleaners, etc...) and in air conditioning systems (eg: automobile). It is impossible to avoid.

2020, we now have Vaper's lung (EVALI/VALI/VAPI)

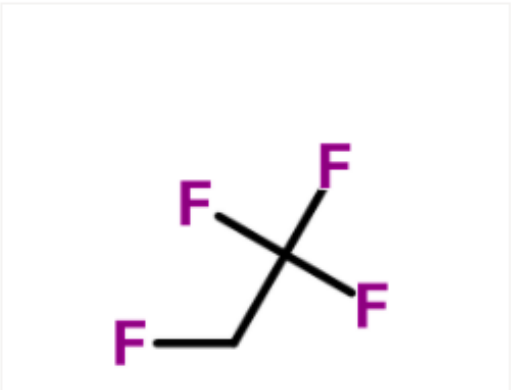


The hypothesis:

Exposure to HFC 134a formulation promotes development of hypersensitivity rxns (Type I – IV & autoimmune)

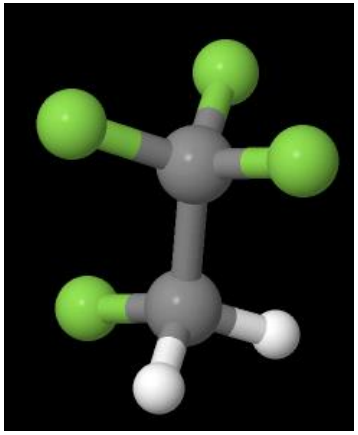
What is HFC 134a (1,1,1,2-Tetrafluoroethane)?

- Produced by Dupont (Chemours), Solvay, Ineos Fluor → Mexichem
- non-toxic
- Eliminated quickly from blood when inhaled
- P450 oxidized metabolites considered to be non-reactive
- Excellent solvent and propellent

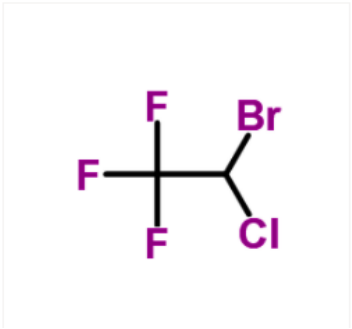


1,1,1,2-Tetrafluoroethane

Molecular Formula	$C_2H_2F_4$
Average mass	102.031 Da
Monoisotopic mass	102.009262 Da
ChemSpider ID	12577

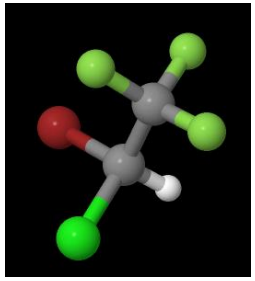


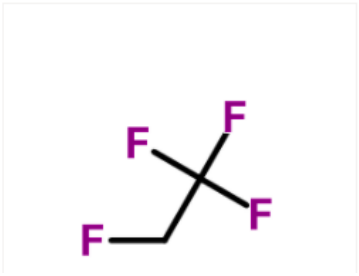
HFC134a is structurally similar to anesthetic haloethane



Halothane

Molecular Formula	$C_2HBrClF_3$
Average mass	197.382 Da
Monoisotopic mass	195.890213 Da
ChemSpider ID	3441





1,1,1,2-Tetrafluoroethane HFC 134a

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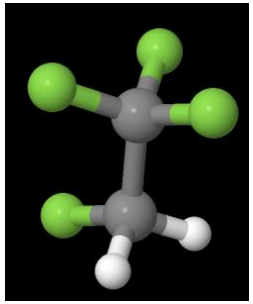


Haloethane is capable of forming a reactive aldehyde (after oxidation by P450s) that can then trifluoroacetylate proteins. Trifluoro groups are recognized as foreign by the immune system and can be the basis for both IgE and IgG mediated antibody responses.

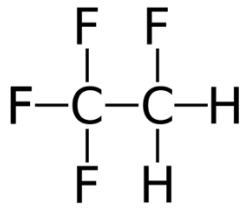
Haloethane/drug rxn researchers think a hypersensitivity response to trifluoroacetylated proteins is what leads to the rare DRESS response (the reason haloethane was taken off the market)

Haloethane anesthetic taken off market due to rare DRESS response

Anesthesiology
69:833–838, 1988

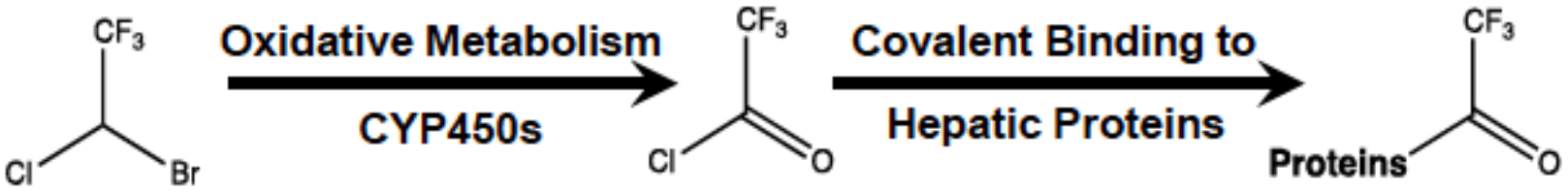
Enflurane Metabolism Produces Covalently Bound Liver Adducts Recognized by Antibodies from Patients with Halothane Hepatitis

David D. Christ, Ph.D.,* J. Gerald Kenna, Ph.D.,† William Kammerer, M.D.,‡ Hiroko Satoh, Ph.D.,§ Lance R. Pohl, Pharm.D., Ph.D.¶

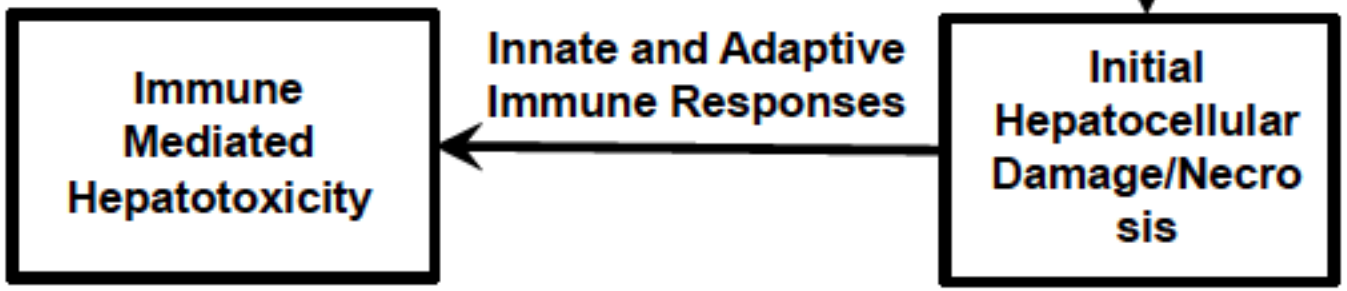


Halothane

Trifluoroacetyl Chloride



Reactive aldehyde



But HFC134a should be relative inert and not form a reactive aldehyde like haloethane. So what could be the mechanism?

One possibility came to me reading a note from a clinician that noticed when patients were administered albuterol via metered inhaler during anesthesia, the gas showed up as haloethane on their monitor.

They did not use haloethane in their hospital (as it was taken off the market many years prior due the DRESS response). The authors concluded the haloethane reading was due to the similar structure of HFC 134a to haloethane.

Letters to Editor

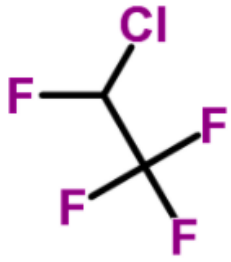
proximal aspect of the standard endotracheal tube (ETT) connector for direct drug delivery to the tracheobronchial tree by puffs for treatment of bronchospasm. All these inhalers have a propellant, which aids in drug delivery. One such propellant, HFA 134a (hydrofluoroalkane: 1,1,1,2 tetrafluoroethane), is the prime suspect in our current case scenario, discovered while giving general anaesthesia through our Dragus Primus® workstation (Scio four Oxi-plus module).

"A bright red rectangle with halothane printed in black popped on the monitor screen. Nothing abnormal, except that **halothane is not available in our operation theatre (OT) for a decade now**. We use only isoflurane, sevoflurane and desflurane as inhalational anaesthetics yet the machine was **falsely reading halothane**."

From talking with several spectroscopists, they thought it was highly unlikely the instrument could confuse HFC-134a and haloethane, but that haloethane and **HCFC 124** (a common impurity in HFC 134a preparations) might be indistinguishable.

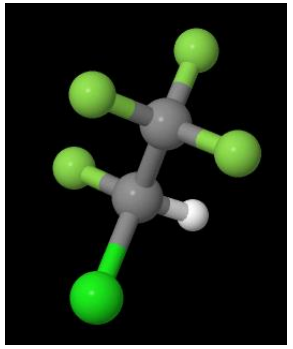
Haloethane and **HCFC 124** (a common impurity in HFC 134a preparations) differ only by a Br vs a Fl and could be indistinguishable by low res IR spectroscopy

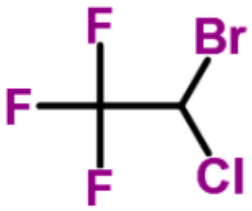
HCFC 124
(impurity)



1,1,1,2-tetrafluoro-2-chloroethane

Molecular Formula	C_2HClF_4
Average mass	136.476 Da
Monoisotopic mass	135.970291 Da
ChemSpider ID	16841





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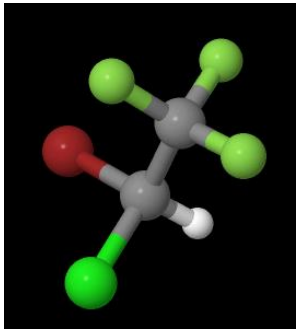

HFC 134a

1,1,1,2-Tetrafluoroethane

Molecular Formula	$C_2H_2F_4$
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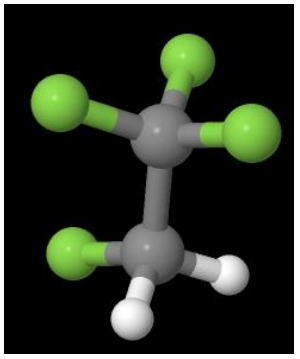
Monoisotopic mass	102.009262 Da
ChemSpider ID	12577



There is (documented) large batch-to-batch variability in the presence of HCFC124 in production of HFC 134a

HCFC-124 is found at variable concentrations in the starting material for generating the purified propellant - it used to be a problem impurity, and companies like Solvay (who produce HFC 134a for metered dose inhalers along) claim they have been able to reduce its presence to undetectable levels.

Chlorofluorocarbons Alternatives Analysis, Part I: The Determination of HFC-134a Purity by Gas Chromatography

D.G. Gehring*, D.J. Barsotti, and **H.E. Gibbon**
Fluorochemicals Laboratory, CW, DuPont Company, Deepwater, New Jersey 08023

- HFA 134 purity varies by batch
- HCFC 124 has immune reactive potential

Table II. Impurities Analysis for Typical Samples*

	ppm Wt.					
Impurity	Cylinder 1	Cylinder 2	Cylinder 3	Cylinder 4	Cylinder 5	Cylinder 6
23	<4	<4	<4	8	<4	<4
143a	32	1	44	152	<1	<1
152a	1	10	13	<1	<1	<1
1234yf	<1	1	<1	4	<1	2
12	<2	<2	<2	<2	5	403
124	921	47	124	2	16	6
114	<2	<2	<2	<2	14	21
114a	67	78	77	2	3	5
134	884	<2	15	4	82	64
1122	<1	<1	2	26	2	8
125	9	<2	<2	109	<2	96
115	<5	<5	35	<5	<5	15
1123	<1	<1	<1	2	14	21
133a	<1	<1	<1	<1	3	<1
1336mzz	<1	<1	<1	<1	2	<1
Purity %	99.897	99.986	99.971	99.970	99.994	99.942

* Note: 134 included with 134a for purity reporting.

Table II. Recommended Assay and Impurities Acceptance Criteria for HFA-134a Propellant

Impurity	HFA-134a Acceptance Criteria (ppm)	Impurity	HFA-134a Acceptance Criteria (ppm)
HCC-40	5	HCFC-133a	5
HFC-23	5	HCFC-161	30
HFC-32	5	HCFC-1121	5
HFC-125	5	HCFC-1122	5
HFC-134	1000	HCFC-1122a	5
HFC-143a	10	CFC-11	5
HFC-152	5	CFC-12	100
HFC-152a	300	CFC-12B1	5
HFC-245cb	5	CFC-13	5
HFC-1123	5	CFC-113	5
HFC-1132	5	CFC-114	5
HFC-1225ye	5	CFC-114a	25
HFC-1234yf	5	CFC-115	5
HFC-1243zf	5	CFC-1112a	5
HFC-1336mzz	5	FC-1318my-T	5
HCFC-22	50	FC-1318my-C	5
HCFC-31	5	Total unsaturates (including HCFC-1122)	5
HCFC-123	5	Individual unidentified impurities	5
HCFC-123a	5	Total unidentified impurities	10
HCFC-124	100	Other organic impurities	50
HCFC-124a	5	Any other identified saturated impurity	5
HCFC-132b	5	Total impurities	1000
		Assay	99.9%

11.APR.2000 18:04 SOLVAY FLUOR & DERIVATE GMBH NR.505 S.2/6

code	formula	Solvay (draft FDA) spec ppm (v/v)
CFC-11	CCl3F	- (5); not present
CFC-1112a	CF2=CCl2	- (5); not present
CFC-113	CCl2F-CClF2	- (5); not present
CFC-114	CClF2-CClF2	- (5); not present
CFC-114a	CCl2F-CF3	10 (25); present only in raw material
CFC-115	CClF2-CF3	5 (5); present only in raw material < 1ppm
CFC-12	CCl2F2	5 (100); present only in raw material < 1ppm
CFC-12B1	CClBrF2	- (5); not present
CFC-13	CClF3	5 (5); present only in raw material < 0,5 ppm
CFC-217ba	CF3-CClF-CF3	5 (-); present
FC-1318my-C	CF3-CF=CF-CF3 c	5 (5); present
FC-1318my-T	CF3-CF=CF-CF3 t	5 (5); present
HCC-1120	TRI	5 (-); present in traces < 0,3 ppm; starting material
HCC-30	CH2Cl2	5 (-); present in traces < 0,3 ppm
HCC-40	CH3Cl	5 (5); present only in raw material
HCFC-1121	CHCl=CClF	- (5); not present
HCFC-1122	CHCl=CF2	5 (5); present
HCFC-1122a	CHF=CClF	5 (5); present
HCFC-1131	CHF=CHCl	5 (-); present
HCFC-123	CHCl2-CF3	- (5); not present
HCFC-123a	CHClF-CClF2	- (5); not present
HCFC-124	CHClF-CF3	10 (100); present only in raw material
HCFC-124a	CHF2-CClF2	- (5); not present
HCFC-132b	CClF2-CH2Cl	- (5); not present
HCFC-133a	CH2Cl-CF3	5 (5); present
HCFC-22	CHClF2	5 (50); present only in raw material < 1ppm
HCFC-31	CH2ClF	5 (5); present only in raw material < 1 ppm
HFC-1123	CHF=CF2	- (5); not present !
HFC-1132	CHF=CHF	5 (5); present
HFC-1225ye	CHF=CF-CF3	5 (5); present only in raw material
HFC-1234yf	CH2=CF-CF3	5 (5); present only in raw material
HFC-1243zf	CH2=CH-CF3	5 (5); present
HFC-125	CHF2-CF3	5 (5); present
HFC-1336mzz	CF3-CH=CH-CF3	- (5); not present
HFC-134	CHF2-CHF2	100 (1000); present
HFC-134a	CH2F-CF3	CP: 99,9% (v/v)
HFC-143a	CH3-CF3	10 (10); present
HFC-152	CH2F-CH2F	- (5); not present
HFC-152a	CH3-CHF2	5 (300); present
HFC-161	CH2F-CH3	- (30); not present
HFC-23	CHF3	- (5); not present
HFC-245cb	CF3-CF2-CH3	5 (5); present only in raw material
HFC-32	CH2F2	- (5); not present

Specification Solkane 134a pharma based on the first 5 batches manufactured on pilot scale April 11, 2000

- **4 impurities added** (217ba, HCFC-1131, HCC-30 and HCC-1120)
- ***16 impurities not present; not even in the raw material*** (CFC-11, CFC-1112a, CFC-113, CFC-114, CFC-12B1, HCFC-1121, HCFC-123, HCFC-123a, HCFC-124a, HCFC-132b, HFC-1123, HFC-1336mzz, HFC-152, HFC-161, HFC-23, HFC-32)
- **11 impurites present only in the raw material** (CFC-114a, CFC-115, CFC-12, CFC-13, HCC-40, HCFC-124, HCFC-22, HCFC-31, HFC-1225ye, HFC-1234yf, HFC-245cb)
- **16 impurities present** (CFC-217ba, FC-1318my-c, FC-1318my-t, HCC-1120, HCC-30, HCFC-1122, HCFC-1122a, HCFC-1131, HCFC-133a, HFC-1132, HFC-1243zf, HFC-125, HFC-134, HFC-134a, HFC-143a, HFC-152a)

Companies appealed to the FDA to be exempted from monitoring for presence of impurities based on the well documented "toxicological" safety of HFA 134a. I have been unable to locate the current FDA reporting requirements for purity of HFC 134a (pharmaceutical or that used in air conditioning for example). Hopefully someone at FDA can do this.

It appears the FDA never set more than a "guideline" in the first place because of the GRAS status of CFCs and later HFCs. When the switch to HFC's happened in the early 2000's (because of the Montreal Protocol) there may have been some regulatory balls dropped.

Electronic Mail Message

Date: 4/25/00 2:20:15 PM
From: Neugebauer, Kenneth (Kenneth.Neugebauer@solvay.com)
To: 'Chamberlinn@cder.fda.gov' (Chamberlinn@A1)
Cc: Pischtiak, Anja (Anja.Pischtiak@solvay.com)
Cc: Neugebauer, Kenneth (Kenneth.Neugebauer@solvay.com)
Subject: 4 minute Presentation to Advisory Committee for Orally inhaled an d nasa

Nancy:

Sorry for the delay, but due to travel and inoperative e-mail system I am only now able to forward the following Statement which I intend to Present during my 4 minute time allocation:

I have not timed it yet. I will shorten it if needed in order to run no more than 3 minutes give or take a few ums, uhh's, and coughs.

I will present an streamlined version of the following:

My name is Ken Neugebauer and I am Director of Marketing and Sales for Solvay Fluorides responsible for the NAFTA Regional Business Unit. I am speaking on behalf of and presenting the comments of:

Ms. Anja Pischtiak
Product Manager Pharmaceutical Aerosols
Solvay Fluor, SFD-KP, Hans-Böckler-Allee 20, 30173 Hannover, Germany
Tel.: +49 (511) 857-3448; Fax: +49 (511) 857-2146; e-mail:
anja.pischtiak@solvay.com

I ask that questions related to these comments be submitted in writing for response by Ms. Pischtiak.

"Solvay Fluor as a manufacturer of the propellants HFA 227 and HFA 134a used in inhalation drug products, marketed by Solvay under the tradenames Solkane®
227 pharma and Solkane® 134a pharma, would like to make two comments on the major excipients in MDIs, the noncompendial propellants HFA 227 and HFA 134a. The comments relate to the Draft Guidance for Industry - Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products - Chemistry, Manufacturing, and Controls Documentation:

1. Lines 288 to 295 identify a requirement for a toxicological qualification of the novel excipients HFA 134a and HFA 227 but do not give directives of what comprises a toxicological qualification.
The consortia IPACT-I and IPACT-II (IPACT = International Pharmaceutical Aerosol Consortium for Toxicology Testing) already have submitted to the FDA extensive safety data on HFA 134a (generated and submitted by IPACT-I) and HFA 227 (generated and submitted by IPACT-II) intended for inhalation which may sufficiently demonstrate the toxicological suitability of the novel excipients HFA 134a and HFA 227 for use in medical products, incl. MDIs. Solvay believes that the uncertainty on the requirements for a toxicological qualification of the pure excipients stops the pharmaceutical industry from reformulating its CFC containing products using HFAs and therefore proposes to add a definition for the toxicological qualification of the noncompendial propellants HFA 134a and HFA 227.

2. Lines 381 to 405 show impurity acceptance criteria limits for HFA 134a impurity by impurity, which are, given in such a detail, process related. Solvay, for example uses for the manufacture of Solkane 134a pharma a process starting from trichloroethylene, which is not mentioned in the FDA specification, but is present in trace but detectable amounts (at concentrations of < 1 ppm) in
Solkane 134a pharma and therefore are specified by Solvay. While Solvay has four additional impurites not shown in the specification quoted by the FDA, other impurities which are listed in the Draft Specification are not contained in Solkane 134a pharma.
Therefore Solvay proposes to replace detailed impurity-by-impurity limits by acceptance criteria based on toxicological tests performed, both for HFA 134a and for HFA 227."

In addition I am submitting with these comments Solvay's Specifications of Solkane® 134 pharma with detailed description of the differences in comparison with the Draft Guidance 134a specification.

Additionally I submit the Specification for Solkane® 227 pharma as filed with the FDA in our DMF - to be added to the Draft Guidance in case the 134a Specification remains.

Finally, Solvay agrees in principle with comments previously submitted by IPAC as published in the August 1999 " Gold Sheet " and are submitted again here with key points highlighted.

Thank you.

Mit freundlichen Grüßen / meilleures salutations / Best regards,
> Ken Neugebauer
> Director of Sales/Marketing - Inorganic Fluorides, Manager TQM
> Solvay Fluorides, Inc. 41 W. Putnam Ave, Greenwich CT 06830
> phone: (203) 629-7900 Fax: (203) 629-9074
> e-mail:mailto:kenneth.neugebauer@solvay.com web:
> http://www.solvay-fluor.com http://www.solvay.com
>
>

Comments to Draft Guidance for Industry (MDI's)

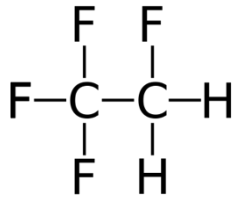
- Add a definition for the toxicological qualification of the noncompendial propellants HFA 134a and HFA 227 - promotes accelerated CFC phaseout.
- Establish acceptance criteria based on toxicological test results for 134a and 227 propellants instead of using detailed impurity by impurity limits which are process / producer dependent.

HCFC-124, similar to haloethane, can be converted to a reactive aldehyde by P450s and in this form would be capable of trifluoroacetylating proteins (or other molecules).

If HCFC 124 is present and promoting disease, my guess is that unlike haloethane (maybe the absence of the bromine) this is done by P450s present along mucosal surfaces (lung, GI tract) and where exposure is greatest (inhalation, ingestion), rather than going to the liver (as haloethane does). I think CYP2E1 is a likely candidate because of the location of the symptoms of eosinophilic asthma and EPGA, and because of the leydig tumors seen in the toxicology studies on mice exposed to high doses of R134a.

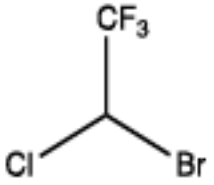
TISSUES WHERE **CYP2E1** is expressed

lungs, mucosal surfaces, GI tract, kidneys



Halothane

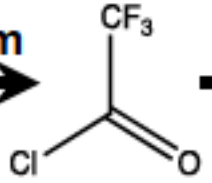
Trifluoroacetyl Chloride



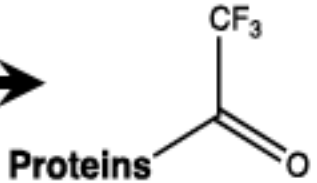
Oxidative Metabolism

CYP450s

CYP2E1 ?

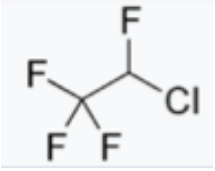


Covalent Binding to Hepatic Proteins



Reactive aldehyde

HCFC 124



Initial Hepatocellular Damage/Necrosis

Innate and Adaptive Immune Responses

Immune Mediated Hepatotoxicity

For HCFC124, development of Type I-IV hypersensitivity reactions and autoimmune disease: eosinophilic pneumonia, acute hypersensitivity pneumocystis, DRESS-like responses, hypereosinophilic syndrome, Churg-Strauss, asthma, eosinophilic GI disease, etc….

The take-home messages

Studies on the safety of R134 primarily focused on toxicology. There is a clear connection between developing hypereosinophilic syndrome/Churg-Strauss/EPGA and inhaled corticosteroids; this is often written off as *forme fruste* (ie the individuals taking the inhalers were on the road to disease regardless), but this does not explain half the cases of people that were never on oral steroids, indicating that this hypothesis is either incorrect or incomplete.

Even if this is all very unlikely (that the propellant is causing pathology) AND it goes against the dogma that the propellants are safe (totally open to this idea), I feel a responsibility as a scientist to push this issue. When the toxicity studies were performed, no one was thinking about allergy (or autoimmunity), which could take years to develop, especially given the low daily exposure and volatility of the substances and the relative rarity with which people develop allergy. There is more than enough data out there to make a case for investigating further, and this is based only on research I have done as a non-expert in the field.

If the propellent/solvent is leading to allergic responses it seems to have mostly Type I characteristics for eosinophilic asthmatics, but I think for at least some people that have more systematic eosinophilic symptoms (eg. the idiopathic hypereosinophilic variety, EPGA, and some of the pneumonias seen in EVALI cases), there is a possibility that they have developed a delayed-type hypersensitivity reaction (or combination of Type III/Type IV) that seems to mainly affect mucosal surfaces following inhalation/ingestion (lung, GI, skin). I've been thinking about iHES/EPGA because of the epidemiological data, but given the proposed mechanism (more on that below), this could be generalizable to other immune-based, including autoimmune diseases (celiac, lupus, scleroderma, hypothyroiditis, etc).

My major concern is asthmatics because of the chronic daily exposure (inhaled steroids are usually taken morning and night, with albuterol as-needed). However, now **everyone** has access to over-the-counter metered nose spray (eg. **Flonase**), and this has me particularly concerned - especially for anyone using them long term (months-->years). Now there is Children's Flonase (for age 4+). Sometimes this stuff keeps me up at night. Should we be taking these risks before more studies when there are nebulizers and powder-based inhalers available? I also worry that the introduction of HFC 134a into the food supply is a giant, potentially scary experiment.

The lung vaping disease presents as diverse pneumonias, suggesting there is not a single etiology. This is inconsistent with the idea that Vitamin E acetate itself is responsible for the pneumonias (Tocopherols, btw, can also be extracted with R134a). Moreover, there is a very obvious connection to R134a and the extraction of cannabinoids. Some individuals in the threads alluded to using **R134a intended for car air conditioners** (expected to have much more of the **HCFC 124** impurity) The cases are generally acute and respond to corticosteroids, consistent with development of severe allergy.

Please forward this communication to anyone you know that might be able to look into this further – including physicians. At a minimum it will plant a seed; an extra variable to consider and be cognizant of when treating patients. Even if the hypothesis is incorrect and everything turns out to be safe, it will do no harm.

What about Vitamin E acetate?

How (from a mechanistic standpoint) the Vitamin E acetate could directly cause all of the observed pathologies is quite unclear to me. I am open to this hypothesis, but it leaves many questions unanswered.

1) Why is EVALI rare compared to the number of vapers? (even among those using illicit THC). People use the language “a bad batch” but is a bad batch any oil with Vitamin E acetate? If that is the case, why do some individuals using identically sourced products (including the same batches of CBC oils) develop illness but not others? (I think this suggests it is not an irritant and is instead consistent with the development of hypersensitivity in only a subset. Developing an aller)

2) How does one account for the nicotine-only cases? (10-33% depending on reports, more in Canada) - one has to assume that 100% of those individuals were dishonest about use their use of illicit substances. I concede some certainly were, but 100% seems highly unlikely.

3) Why do there appear to be different kinds of lung disease (sometimes eosinophilic pneumonia, sometimes hypersensitivity pneumonitis, sometimes lipoid-like pneumonia, etc…. My hypothesis is that it is due to the different types of hypersensitivities that develop (and the mechanism I propose accounts for that).

From scanning the news, a large sector of the public (especially the vaping public) and the tobacco industry have decided that Vitamin E acetate is the culprit compound, and they are extremely unhappy that the FDA/CDC will not use language to concede this point. While it is strongly correlated, I am not yet convinced. It could be correlated for the simple reason that producers using R134a to extract cannabinoids also generally also use(d) Vitamin E acetate as a cutting agent. It’s potentially dangerous not to account for the discrepancies in the current hypothesis (THC & VitE acetate) going forward.

The dearth of regulation on devices and ingredients (**especially flavorings**) in legal products & has me concerned.