UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARKEMA INC. & ARKEMA FRANCE
Petitioners

v.

HONEYWELL INTERNATIONAL, INC.
Patent Owner

Case Nos. IPR2016-00643
PGR2016-00011
PGR2016-00012

Patent No. 9,157,017

DECLARATION OF WILLIAM J. BROCK, PH.D., DABT, FELLOW ATS

Contents

I. INTRODUCTION

1. I, William J. Brock, Ph.D., DABT, FELLOW ATS, have been retained by Finnegan, Henderson, Farabow, Garrett, & Dunner, LLP ("Finnegan") on behalf of Arkema Inc. and Arkema France (collectively "Arkema") as an expert in toxicology, in general, and especially in the area of refrigerant compounds. My qualifications in this area, as well as other areas, are established by my curriculum vitae, which is attached as Appendix A.

II. QUALIFICATIONS

2. I have over 30 years of experience as a toxicologist in research and development in the chemical, pharmaceutical, consumer product, food products, and medical device industries. My curriculum vitae is attached as Appendix A.

3. I received a B.S. in chemistry and biology from Geneva College in 1976, and received a Masters and Ph.D. in toxicology from the University of Kentucky in 1980 and 1983, respectively. I continued at the University of Kentucky as a post-doctoral fellow until June 1983.

4. After receiving my Ph.D. and completing my post-doctoral fellowship, I became employed by DuPont at Haskell Laboratory for Toxicology and Industrial Medicine (now Haskell Laboratory for Health and Environmental Sciences). As a toxicologist, I was responsible for the safety evaluation of numerous substances including pharmaceuticals, food additives, agrochemicals,

and commodity chemicals; toxicity testing recommendations; toxicity study design and monitoring; and representing DuPont on national and international toxicology committees.

5. During my tenure at DuPont's Haskell laboratory, I supervised (as a Study Director) the conduct of many toxicology studies that utilized the dog, rat, mouse, rabbit, and other species routinely used for the safety evaluation of substances. The duration of those studies consisted of single dose, subchronic (up to 3 months) and chronic (up to 1 year) studies.

6. In 1999, I became the Director for Scientific Affairs at Unilever. In that position, I was responsible for the safety assessment of personal care products, food ingredients, and drug products, primarily over-the-counter (OTC) drug products.

7. In 2002, I joined the international consulting firm, Environ. At Environ, I began to develop a toxicological practice assisting clients with the evaluation of substances, including commodity chemicals, medical device ingredients, and food ingredients. In 2010, I joined Otsuka Pharmaceuticals as the Associate Director of Toxicology in the department of Nonclinical Drug Safety and became the Director of Toxicology in 2013. I resigned from Otsuka in August 2015.

8. In 2004, I became an independent consultant at Brock Scientific Consulting, LLC. The primary focus of my consulting practice is to assist clients in the pharmaceutical industry. As an independent consultant, I continue to design and oversee the conduct and reporting of toxicology studies that utilize multiple species and multiple routes of administration on behalf of clients.

9. I am certified in general toxicology by the American Board of Toxicology (ABT) and recognized as a Fellow by the Academy of Toxicological Sciences (ATS). I served on the Board of Directors and as President for both certifying organizations.

10. I served as a member and in a leadership capacity for several national and international toxicology organizations including the Society of Toxicology; American College of Toxicology; Drug Information Association; American Chemistry Council; International Pharmaceutical Excipient Council Expert Review Panel; American Society of Heating, Refrigerating and Air-Conditioning Engineers Toxicology Standards Committees; and National Toxicology Program.

11. I have been an invited speaker to the Committee on Toxicology, National Research Council, International Pharmaceutical Excipient Council, the government of China, and other professional organizations and universities to provide lectures on various toxicological topics.

12. I have an appointment as an adjunct associate professor at the University of North Carolina, Chapel Hill in the Eshelman School of Pharmacy. Also, I had previous adjunct appointments at West Chester University and the University of Medicine and Dentistry of New Jersey.

13. I have authored or co-authored seven book chapters on toxicology, and have co-edited two books on toxicology and international pharmaceutical regulations for nonclinical scientists. I have over forty peer-reviewed publications and have presented or co-presented over approximately forty abstracts at toxicology meetings.

14. I am an Associate Editor for the International Journal of Toxicology, serve on the editorial board for Toxicology and Industrial Health, and periodically review submitted manuscripts for other peer-review toxicology journals including Toxicological Sciences, Food and Chemical Toxicology, Current Eye Research, Journal of Applied Toxicology, and other leading toxicology journals.

III. PREVIOUS TESTIMONY AND COMPENSATION

15. I was paid a consulting fee of $300 per hour for my time to research and prepare this declaration. My compensation is not dependent in any way on the outcome of the proceeding.

IV. MATERIALS CONSIDERED

16. In forming my opinions, I have had available the materials cited in this report, Arkema's petitions, as well as those listed in the attached Appendix B. In addition to these materials, I may consider additional documents and information in forming any supplemental opinions. To the extent I am provided with additional documents or information, including any expert declarations in this proceeding, I may offer further opinions.

V. SUMMARY OF OPINIONS

17. I have been asked by Finnegan on behalf of Arkema to consider U.S. Patent No. 9,157,017 (Ex. 1001, "the '017 patent") and prior art[1] related to it, and to offer my opinions in the area of toxicity on the effect of that art on the claims of the '017 patent.

18. In preparing this declaration, I have been educated generally on relevant patent law issues, including the standards for obviousness.

19. I understand that a patent claim is obvious if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

[1] I have been asked to assume, for the purposes of my evaluation, that documents dated before October 25, 2002, are prior art to the '017 patent.

20. I have been informed that obviousness cannot be avoided simply by showing some degree of unpredictability in the art so long as there was a reasonable probability of success. I have also been informed that only a reasonable expectation of success, not a guarantee, is needed.

21. I have also been advised that certain factors known as "secondary considerations" of non-obviousness must be considered if put forward by the patentee. I understand that these include, but are not limited to, unexpected results, failure by others, and skepticism by experts, commercial success, and long-felt but unmet need.

22. I have been informed that when unexpected results are used as evidence of non-obviousness, the results must be shown to be unexpected compared with the closest prior art. I have also been informed that evidence presented to rebut a *prima facie* case of obviousness must be commensurate in scope with the claims to which it pertains and that the court must consider what properties would have been expected.

23. With this understanding, it is my opinion that a person of ordinary skill in the art prior to October 2002 would have had a reasonable expectation that R-1234yf would be low in toxicity with no substantial acute toxicity, and as a

result it would have been obvious to further develop R-1234yf for automotive air conditioning ("AAC") applications.[2]

24. It is further my opinion that the allegedly unexpected toxicity properties presented by Honeywell during the prosecution of the '017 patent are not, in fact, unexpected and are entirely predictable based on the analysis a person of skill in the art would have undertaken prior to October 2002.

VI. DEFINITION OF A PERSON OF ORDINARY SKILL IN THE ART

25. I understand that Dr. Brown, an expert in refrigerants and heat transfer compositions, has opined that a person of ordinary skill in the relevant art—that is one who evaluates, designs, and develops new refrigerants for use as heat transfer fluids—would generally possess a Ph.D. in Chemistry, Chemical Engineering, Mechanical Engineering, Material Science, or in a related field or discipline and would have at least 3 to 5 years of experience in the design, development, and/or modeling of refrigerants, or alternatively such an individual would have a M.S. degree in one of those fields with 5 to 10 years of experience in the refrigerant industry. A person of ordinary skill in the art also would have experience with or access to other individuals with knowledge and experience in the design, evaluation, and selection of lubricants as well as the toxicology of refrigerants. I adopt this definition.

[2] Throughout this declaration, I use R-1234yf and HFO-1234yf interchangeably.

26. As a toxicologist who has worked closely with persons of ordinary skill in the art as defined above, it is my opinion that such persons would have a toxicologist available to him or her during the evaluation, design, and development of refrigerants. It is my opinion that one of ordinary skill in the art in the field of toxicology would possess a Ph.D. in toxicology or related sciences coupled with at least 3 years of experience with toxicity testing and the evaluation of the results of toxicity testing of hydrofluorocarbons. Alternatively, the person of ordinary skill in the art may possess a M.S. in toxicology or related sciences coupled with at least 7 years of experience with toxicity testing and the evaluation of the results of toxicity testing of hydrofluorocarbons.

VII. CLAIM CONSTRUCTION

27. For the purposes of this proceeding, I have construed the claims as a person of ordinary skill in the art based on the claim language when read in view of the specification. I understand that in post-grant proceedings the claims are construed according to their broadest reasonable interpretation. The constructions provided herein are based on that standard. I note, however, that my opinions in this declaration do not change if broader or narrower constructions are adopted during this proceeding.

A. "low toxicity refrigerant suitable for use in automobile air conditioning"

28. Claims 1, 6, 12, and 19 states "low toxicity refrigerant suitable for use in automobile air conditioning." (Ex. 1001 at Claims 1, 6, 12, 19.) The broadest reasonable construction of this phrase, when read in light of the specification, means "**a refrigerant that has low acute toxicity as measured by inhalation exposure to mice or rats**." This is consistent with the specification, which states that "applicants believe that a relatively low toxicity level is associated with compounds of Formula II, preferably wherein Y is CF_3, wherein at least one R on the unsaturated terminal carbon is H, and at least one of the remaining Rs is F." (*Id.* at 4:38-42.) This construction is also consistent with the specification's only other disclosure related to toxicity, specifically: "in highly preferred embodiments, especially embodiments comprising the low toxicity compounds described above, n is zero in which the unsaturated terminal carbon has not more than one F substituent. Applicant has discovered that such compounds have a very low acute toxicity level, as measured by inhalation exposure to mice and rats." (*Id.* at 4:45-50.) Reading that passage, a person of ordinary skill in the art would have understood the reference to mice or rats refers to acute inhalation toxicity testing with mice and rats as they are used almost exclusively for such testing, as often no other animals are used.

29. As I have construed this phrase, it does not require a specific chronic toxicity level. Although Honeywell argued during prosecution that "in order to be acceptable for use in conventional [AAC] at the time of the present invention, a refrigerant must be Class A toxicity," which takes into account both acute and chronic toxicity data (Ex. 1050 at 11), there is nothing in the specification itself that indicates Honeywell was even considering chronic toxicity at the time it originally filed its applications. Thus, a person of ordinary skill in the art reading the claims in view of the specification would not understand them to set any particular standard with respect to chronic toxicity.

B. "no substantial acute toxicity as measured by inhalation exposure to mice and rats"

30. Dependent claims 4, 9, 16, and 20 recite the limitation "no substantial acute toxicity as measured by inhalation exposure to mice and rats." The specification does not provide any indication what is meant by this phrase, nor does the specification equate any particular LC_{50} to "no substantial acute toxicity." The phrase is also not uniquely defined in the toxicology art. As a result, under the broadest reasonable interpretation, it is my opinion that the relative term "no substantial" should be given its common and ordinary meaning.

31. In this case, without conceding that the term is definite, this phrase means "essentially no acute toxicity level as measured by inhalation exposure to mice and rats."

VIII. DETAILED STATEMENT OF OPINIONS

A. Toxicity Testing of Refrigerants

32. As part of my analysis, I have considered the ’017 patent. I understand that the claims of the ’017 patent are directed to heat transfer compositions (and their uses in AAC) “consisting essentially of: (i) at least about 50% by weight of a *low toxicity refrigerant suitable for use in automobile air conditioning systems*, said refrigerant consisting essentially of 2,3,3,3-tetrafluoropropene (HFO-1234yf); and (ii) lubricant consisting essentially of polyalkylene glycol(s).” (*E.g.*, Ex. 1001 at 18:37-43 (emphasis added).)

33. In the evaluation of the toxicity profile of a material such as a gas, volatile substance, or aerosol/particulate, determination of acute inhalation toxicity is an important initial step. Beyond this, a further toxicity profile can include various other toxicity tests, such as subchronic inhalation studies, mutagenicity studies, and chronic exposure tests. With respect to the conduct of acute inhalation studies, there are international guidelines published by governmental and non-governmental organizations including the U.S. Environmental Protection Agency (EPA) and the Organization for Economic Cooperation and Development (OECD), e.g., EPA 870.1300 and OECD Test Guideline 403.

34. In an acute inhalation toxicity study, different groups of experimental animals, typically mice or rats, are exposed to the test substance for a defined

period of time in graduated concentrations to develop a dose-response relationship. One concentration is most often examined per group of experimental animals. Selection of the initial concentration is determined by consideration of data available either for the particular substance or for structurally-related substances. Controls are not usually used in acute inhalation toxicity studies. During and following exposure, the animals are observed for toxicological effects and mortality. Animals that die during the test are necropsied as soon as possible. The abdominal and thoracic cavities in these dead animals are examined to identify any possible target organ toxic effects. At the conclusion of the observation period, usually 14 days, test animals that survive are humanely sacrificed and necropsied.

35. The exposure duration in an acute inhalation toxicity study is usually 4 hours, although shorter or longer durations are used depending on the purpose of the study.

36. The result of an acute inhalation toxicity study is the LC_{50} (median lethal concentration). It is a statistically derived concentration of a substance that would be expected to cause death in 50% of a population of experimental animals exposed for a specified time. The LC_{50} value is expressed as weight of test substance per standard volume of air (mg/L or mg/m^3) or as parts per million (ppm). The higher the LC_{50} value the less toxic the substance.

37. Another potential result from an acute inhalation toxicity study is the approximate lethal concentration (ALC). The ALC is the lowest concentration of the test substance that results in a single mortality of the exposed animals. This is a measured value. The ALC value is expressed as weight of test substance per standard volume of air (mg/L or mg/m^3) or as parts per million (ppm). This value approximates the LC_{50} of a substance, although the ALC will be lower than the LC_{50}.

38. The data obtained from an acute inhalation toxicity study provides information on the potential human health hazards likely to arise from a single exposure by inhalation.

39. Data from an acute inhalation toxicity study would be used to establish dose levels in subsequent acute and repeat dose toxicity studies.

40. In addition, data from an acute inhalation study may serve as a basis for classifying the toxicity of a compound, for example, "toxic" or "highly toxic."

41. OSHA defines "toxic" and "highly toxic" as follows (29 C.F.R. § 1910.1200 app. A (2002)) (Ex. 1077):

> Toxic. A chemical falling within any of the following categories: . . .
>
> (c) A chemical that has a median lethal concentration (LC_{50}) in air of more than 200 parts per million but not

> more than 2,000 parts per million by volume of gas or vapor, . . .
>
> 3. Highly toxic: A chemical falling within any of the following categories: . . .
>
> (c) A chemical that has a median lethal concentration (LC_{50}) in air of 200 parts per million by volume or less of gas or vapor.

42. These definitions of "toxic" and "highly toxic" were incorporated into ASHRAE Standard 34 (Ex. 1154) by Addendum G to ASHRAE 34-2004.

B. By 2002 A Person of Ordinary Skill in the Art Would Have Predicted a Low and No Substantial Acute Toxicity for HFO-1234yf

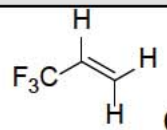
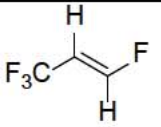
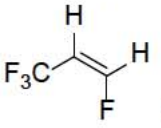
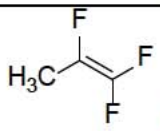
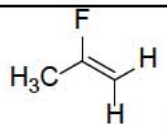
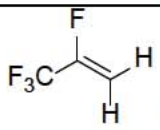
43. In toxicology, one of the first steps in the evaluation of a substance with unknown toxicity, regardless of the end use of the substance, is to evaluate the acute toxicity of the compound. Without any toxicity data for the compound, a toxicologist assisting the skilled artisan would first consider the toxicity of structurally-related halogenated compounds. Structurally-related compounds include, for example, compounds with similar elements, similar numbers of atoms, and similar structures. A toxicologist would also consider any known structure-toxicity relationships. By preparing a hierarchy of known acute toxicity values and evaluating the structures associated with those values, a toxicologist could often

predict, with a reasonable degree of scientific certainty, where the acute inhalation toxicity of a compound would fall within that hierarchy.

44. Prior to 2002, the acute toxicity of many halogenated hydrocarbons was known. In addition, the art established clear correlations between the structure of a compound and its acute toxicity. For example, as will be discussed in detail below, it was well-known in 2002 that replacing a bromine or chlorine atom with a fluorine atom in a compound would generally lead to relatively lower acute toxicity. (Ex. 1141, Clayton 1977 at 256; *see also* Ex. 1140, Clayton 1967 at 225-26.) In addition, by as early as the 1970s, researchers understood that adding electronegative fluorine atoms and trifluoromethyl groups adjacent to a double bond could render a compound more susceptible to nucleophilic attack, increasing the acute toxicity. (*E.g.*, Exs. 1140, Clayton 1967 at 225; 1141, Clayton 1977 at Table 1.)

1. A person of ordinary skill in the art would have expected HFO-1234yf to have acute inhalation toxicity similar to the relatively non-toxic R-1243zf

45. I have reviewed a Japanese Patent Application of Daikin, JP 4-110388, referred to as "**Inagaki**," (Ex. 1012) which discloses a class of about 30 fluoroalkene refrigerants, and includes examples directed to five specific refrigerants, as shown in the following table:

Inagaki Example	Refrigerant	Structure
Example 1	R-1243zf	 **OR** F_3C-CH=CH_2
Example 2	R-1234ze	  **OR** F_3C-CH=CHF
Example 3	R-1243yc	 **OR** H_3C-CF=CF_2
Example 4	R-1261yf	 **OR** H_3C-CF=CH_2
Example 5	R-1234yf	 **OR** F_3C-CF=CH_2

46. As a toxicologist, I consider these compounds to be structurally similar to one another. For example, each compound has three carbon atoms. All but one has three or four fluorine atoms, and all but one has either two or three hydrogens. Moreover, each has a double bond. Thus, at this basic level, a toxicologist assisting a person of ordinary skill in the art to assess the acute toxicity of R-1234yf would have considered the acute toxicity of at least these structurally similar compounds, especially R-1243zf as its acute toxicity was known at the time.

47. In particular, prior to 2002 the acute inhalation toxicity for R-1243zf was known to be low. For example, a 1975 patent states that "[t]rifluoropropene (sic) is flammable, and acute studies indicate it to be relatively non-toxic." (Ex. 1138, Butler at 2:35-36.) In a toxicity study report created in 1965 and submitted to the EPA by Dow Corning in 1991, R-1243zf is specifically reported as having an acute toxicity LC_{50} value of approximately 315,000 ppm. (Ex. 1139, Dow Corning Report dated 1965, submitted to EPA in 1991.) Compared to the OSHA classification for something having an LC_{50} value of between 200 ppm and 2,000 ppm, this value is significantly higher. Based on that and my experience in the field, it is my opinion that an LC_{50} value of 315,000 ppm means that the compound has no substantial acute toxicity as I have construed that term above.

48. R-1234yf is structurally similar to R-1243zf, having only one additional fluorine atom. Based on this structural similarity, a toxicologist of ordinary skill would have expected R-1234yf to have an acute inhalation toxicity that is similar to that of R-1243zf. Thus, considering only the acute inhalation toxicity of R-1243zf, a person of ordinary skill in the art, with the assistance of a toxicologist, would have had a reasonable expectation that R-1234yf would likewise "be relatively non-toxic," that is, have "no substantial acute toxicity."

2. Consideration of additional prior art toxicity information confirms that a person of ordinary skill in the art would have expected HFO-1234yf to have low (and no substantial) acute toxicity

a. Fluorochemical compounds

49. Consideration of additional fluorochemical compounds with known acute toxicity values, which a skilled toxicologist would likely have done, confirms my opinion that a person of ordinary skill in the art prior to October 2002 would have reasonably expected that R-1234yf would have low and no substantial acute inhalation toxicity.

50. In the 1960s and 1970s, Clayton and co-workers reported the acute inhalation toxicities of haloalkanes and haloalkenes. (*E.g.*, Exs. 1140, Clayton 1967; 1141, Clayton 1977.) For example, Table 1 of Clayton 1977, reproduced below, reports acute inhalation toxicity values for a series of fluoroalkenes:

Table 1. Inhalation toxicity of several fluoroalkenes.[a]

	Structure	No. F atoms	Acute toxicity for rats[b] ALC, ppm	Acute toxicity for rats[b] LC_{50} ppm
1	$CH_2=CHF$	1	>800,000[b]	—
2	$CF_2=CH_2$	2	128,000	—
			>800,000[c]	—
3	$CF_2=CF_2$	4	—	40,000
4	$CF_3CF=CF_2$	6	—	3,000
5	$(CF_3)_2C=CF_2$	8	0.5, 0.76[d]	—

[a]Data of Clayton (5).
[b]4-hr exposures except where noted.
[c]80% $CH_2=CHF$, 20% O_2; 12.5-hr exposure.
[d]80% $CH_2=CF_2$, 20% O_2; 19-hr exposure.
[e]0.5 ppm exposure was 6 hr; the 0.76 ppm exposure was 4 hr.

51. Although some of the values reported are ALC values instead of LC_{50} values, as mentioned above, an ALC value provides a reasonable estimate of the LC_{50} value for a compound because the compound's ALC value is almost always lower than its LC_{50} value.

52. The data in Table 1 of Clayton 1977 teaches that inserting a fluorine atom on all carbons in a molecule will generally increase the acute inhalation toxicity of the compound. For example, compound 1, which has only 1 fluorine atom per its 2 carbon atoms, has an ALC of greater than 800,000 ppm. In contrast, the completely fluorinated compound 3 with 4 fluorine atoms per its 2 carbon atoms has an LC_{50} value of 40,000 ppm. Although neither is toxic according to OSHA's classification of a toxic compound, the more fluorinated compound is relatively more toxic than the less fluorinated compound. Stated differently, increasing the carbon-to-fluorine ratio generally leads to decreased acute inhalation toxicity. Specifically, looking at compound 3 in Table 1, there are two fluorine atoms on each carbon (C:F of 1:2). That compound possesses a higher acute inhalation toxicity than either of compounds 1 (C:F of 2:1) or 2 (C:F of 1:1) that include hydrogen atoms on at least one of the carbons.

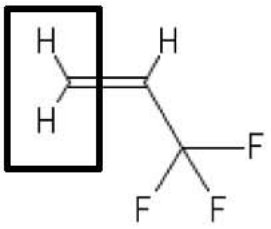
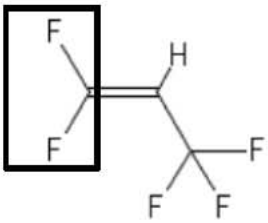
53. In addition, as noted by Clayton in 1967, "[t]he presence of a double bond in the fluorocarbons creates a special chemical environment." (Ex. 1140, Clayton 1967 at 225.) In particular, "[t]he strong electronegative force of opposing

fluoroalkyl groups produces an area of low electron density between adjacent carbons, making the site susceptible to nucleophilic attack." (*Id.*) This means that fluorine atoms tend to pull electron density away from typically electron-rich double bonds. As a result of this shift in electron density, the double bond becomes a potential target for biological nucleophiles, such as –OH and nitrogen-containing groups, which may lead to higher acute toxicity.

54. Accordingly, based on Clayton's teaching regarding the effect of fluorine atoms on the susceptibility to nucleophilic attack of a double bond, a person of ordinary skill before 2002 would have reasonably expected that a compound with fewer fluorine atoms attached to a terminal, unsaturated carbon of a double bond would be less acutely toxic than a compound with one or two fluorine atoms attached to a terminal carbon of a double bond. The compounds in Table 1 of Clayton 1977 demonstrate this very trend.

55. This trend is further demonstrated by comparing the acute inhalation toxicity values of R-1243zf and R-1225zc, which were known prior to 2002. R-1225zc possesses five fluorine atoms and has two fluorine atoms on the terminal unsaturated carbon. In contrast, R-1243zf possesses three fluorine atoms, as well as two hydrogen atoms on the terminal carbon of the double bond. The removal of those fluorine atoms decreased the acute inhalation toxicity of the compound by approximately 150-fold.

Acute Toxicity of R-1243zf and R-1225zc

Name	**R-1243zf (3,3,3-trifluoropropene)**	**R-1225zc (1,1,3,3,3-pentafluoropropene)**
Formula	CH_2CHCF_3	$CF_3CH=CF_2$
Structure		
Acute Toxicity	**Butler** reports that R-1243zf is "relatively non-toxic." (Ex. 1138, Butler at 2:29-39.) **Dow Corning** (Ex. 1139) reported that the 4-hr LC_{50} value is 315,000 ppm	**DuPont** reported a 4-hr LC_{50} value of < 2000 ppm (Ex. 1148, DuPont Haskell Support Letter at A04 (2000))

56. Honeywell's later data relating to R-1225ye, the compound that results when one of the fluorine atoms attached to the terminal unsaturated carbon in compound 4 of Table 1 of Clayton 1977 is replaced with a hydrogen atom, confirms this trend and demonstrates that the very low toxicity of R-1234yf is not unexpected. During prosecution of the '017 patent, Honeywell submitted evidence

that R-1225ye has LC_{50} values of >250,000 ppm in rats, and from 100,000 ppm to 250,000 ppm in mice. (Ex. 1142, Rusch Decl. at ¶¶ 3-6). That is significantly higher (less toxic) than the LC_{50} value for compound 4 in the Clayton 1977 Table 1, which differs structurally in that it has two fluorine atoms on the carbon of the terminal double bond, just as expected. Conversely, when both fluorine atoms bonded to the terminal unsaturated carbon of compound 4 are replaced with hydrogen atoms, R-1234yf results. That compound, as we know, has no substantial acute toxicity, consistent with the expected trend. (Ex. 1143, Honeywell R-1234yf MSDS (the LC_{50} value is >400,000 ppm).)

57. Overall, the aggregate acute inhalation toxicity data of compounds 1-4 of Table 1 of Clayton 1977 demonstrate that acute inhalation toxicity of fluorinated alkenes decreases 1) with decreasing number of fluorine atoms (or increasing C:F ratios) and 2) when fluorine atoms on the carbon of a terminal double bond are replaced by hydrogen atoms.

58. Notably, only the most perfluorinated compound, compound 5, is actually classified as "toxic" according to OSHA standards for acute inhalation toxicity. The remaining compounds, including compound 4, which is similar to R-1234yf except that it has two additional fluorine atoms, would all be classified as having low toxicity according to OSHA standards (LC_{50} >2,000 ppm). In my opinion, a toxicologist prior to October 2002 would have reached these same

conclusions based on Clayton's data and the DuPont's data regarding R-1225zc. A skilled toxicologist would have predicted that R-1234yf would have an acute inhalation toxicity that is much greater than 3,000 ppm (two fewer Fs), likely greater than 40,000 ppm (much lower C:F ratio), and reasonably likely to be similar to the least toxic compounds (more similar C:F ratios), such as compounds 1 and 2 of Clayton 1977 Table 1 and R-1243zf.

b. Related chlorine and bromine containing compounds

59. A toxicologist assisting a person of ordinary skill in the art also would have considered other related halogenated alkene compounds and their corresponding acute inhalation toxicity. In general, substituting a fluorine atom for a chlorine or bromine atom tends to stabilize a compound and thus leads to a compound of lower acute toxicity. Indeed, in 1977, Clayton and coworkers observed that "[g]enerally, fluorinated alkenes are less toxic than chlorinated alkenes." (Ex. 1141, Clayton 1977 at 256; *see also* Ex. 1140, Clayton 1967 at 225-26.) Similarly, Thomas Midgley, the researcher who invented chlorofluorocarbons in the 1920s and 1930s, observed that the toxicity of halocarbons generally decreases with substitution of lighter elements (i.e., hydrogen and fluorine) at the top of the periodic table in place of heavier elements (i.e., bromine and chlorine) at the bottom. (*See* Ex. 1112, Calm & Didion at 7-8.) In Table 3 of Clayton 1977, homologous pairs illustrate this point.

Table 3. Toxicity comparisons among some halogenated alkenes (rats).[a]

	Structure	Acute inhalation toxicity, ALC, ppm (by volume)[b]
1	$CH_2=CHCl$	>250,000[c]
2	$CH_2=CHF$	>800,000[d]
3	$CH_2=CCl_2$	32,000 128,000
4	$CH_2=CF_2$	>800,000[e]
5	$CCl_2=CCl_2$	4,000
6	$CF_2=CF_2$	40,000

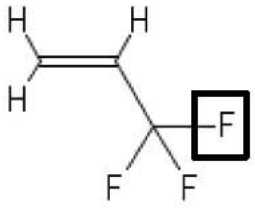
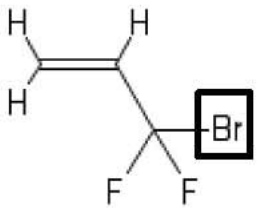
[a]Data of Clayton (5).
[b]All 4-hr exposures except where noted.
[c]Guinea pigs, 8-hr exposure.
[d]80% $CH_2=CHF$, 20% O_2; 12.5 hr exposure.
[e]80% $CH_2=CF_2$, 20% O_2; 19-hr exposure.

60. As can be seen based on the last two compounds (compounds 5 and 6) in Table 3, going from perchlorinated compound 5 to perfluorinated compound 6 leads to a 10-fold decrease in acute inhalation toxicity. I further note that none of the compounds in this table would have been classified as "toxic" according to OSHA guidelines (toxic = 200< LC_{50} <2,000 ppm).

61. Bromine atoms, even more so than chlorine atoms, tends to lead to a compound that is relatively more toxic than its chlorine or fluorine analogs, in that order. For example, Tapscott and coworkers provide information regarding the acute toxicity of 3-bromo-3,3-difluoropropene, a bromine analogue of R-1243zf (LC_{50} >300,000 ppm). 3-Bromo-3,3-difluoropropene, which replaces one of the fluorine atoms with a bromine in R-1243zf, caused 7 of 10 rats to die when exposed to 50,000 ppm for 30 minutes. (Ex. 1015, Tapscott at 212, Table 2.) This indicates that 3-bromo-3,3-difluoropropene is more toxic (30-minute LC_{50} <50,000

ppm) than R-1243zf. Thus, in 2002 a toxicologist would have expected that substitution of a fluorine for a bromine in these compounds would result in lower acute inhalation toxicity.

Acute Toxicity of R-1243zf and 3-bromo-3,3-difluoropropene

Name	**R-1243zf (3,3,3-trifluoropropene)**	**3-bromo-3,3-difluoropropene**
Formula	CH_2CHCF_3	$CH_2CHCBrF_2$
Structure		
Acute Toxicity	**Butler** reports that R-1243zf is "relatively non-toxic." (Ex. 1138, Butler at 2:29-39.) **Dow Corning** (Ex. 1139) reported that the 4-hr LC_{50} value is 315,000 ppm	**Tapscott** reports that 7 of 10 rats exposed to 50,000 ppm for 30 minutes died. (Ex. 1015, Tapscott at Table 2.)

62. Tapscott and coworkers also reported that 2-bromo-3,3,3-trifluoropropene ("2-BTP")—the bromine analogue of R-1234yf—caused no

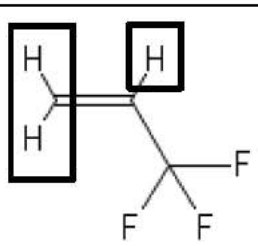
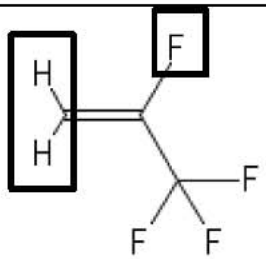
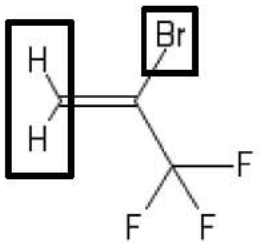
mortality in rats exposed to 50,000 ppm for 30 minutes.[3] (Ex. 1015, Tapscott 2002 at 212.) Tapscott and coworkers noted that "[e]ven at this extremely high concentration [i.e., 5% by volume], half of the compounds tested [including 2-BTP] showed no lethality." (Ex. 1015, Tapscott 2000 at 212.) Tapscott states that these bromofluoroalkene compounds—including 2-BTP—are being considered as replacements for Halons, which are used as total flooding flame suppressants. (*See* Exs. 1015, Tapscott 2000 at 212; 1144, Lifke at 4-5.) This also indicates that 2-BTP has low toxicity because, since total flooding agents are discharged directly into confined spaces (e.g., aircraft) often occupied by humans, they must have very low and no substantial acute toxicity. (*See* Ex. 1144, Lifke at 4-5.) Based on this requirement for low toxicity chemicals for use as flooding flame suppressant agents and the general trend that replacing a fluorine for a bromine decreases acute inhalation toxicity, a person of ordinary skill in the art would have expected R-1234yf to have an acute inhalation toxicity similar to, or even lower than, the low acute toxicity of 2-BTP.

[3] Because no mortalities occurred, it can be concluded that the 30-minute LC_{50} is greater than 50,000 ppm.

3. Reasonable predictions about the acute inhalation toxicity of R-1234yf and related compounds

63. As already mentioned above, a person of ordinary skill in the art prior to October 2002 would have had a reasonable expectation that R-1234yf has low and substantially no acute toxicity. Specifically, a toxicologist would have reasonably predicted that R-1234yf, which has only 4 fluorine atoms, a C:F ratio of 0.75, and no fluorine atoms on the terminal unsaturated carbon, would possess low and substantially no acute inhalation toxicity. In fact, knowing the acute inhalation toxicity of structurally-related compounds, a toxicologist would have predicted that R-1234yf would not be classified as "toxic" according to OSHA guidelines. Moreover, based on what was known prior to October 2002, a toxicologist would expect R-1234yf to be less acutely toxicity than 2-BTP. The two compounds are structurally identical except for a bromine to fluorine replacement, and similar to R-1243zf, which has one hydrogen atom in place of a fluorine on the left side (as depicted below). Acute inhalation toxicity testing of R-1234yf confirms these predictions. The 4-hour LC_{50} value is reported to be >400,000 ppm. (Ex. 1143, Honeywell R-1234yf MSDS.) R-1243zf, 2-BTP, and R-1234yf are shown below:

Structure and Acute Toxicity of R-1243zf, 2-BTP, and R-1234yf

	Butler (Ex. 1138)	**'017 Patent** (Ex. 1001)	**Tapscott** (Ex. 1015)
Compound	R-1243zf	R-1234yf	2-BTP
Name	3,3,3-trifluoropropene	2,3,3,3-tetrafluoropropene	2-bromo-3,3,3-trifluoropropene
Formula	$CH_2=CHCF_3$	$CH_2=CFCF_3$	$CH_2=CBrCF_3$
Structure			
Acute Toxicity	**Butler** reports that R-1243zf is "relatively non-toxic." (Ex. 1138, Butler at 2:29-39.) **Dow Corning** (Ex.	R-1234yf has a 4-hr LC_{50} in rats > 400,000 ppm. (Ex. 1143, Honeywell R-1234yf MSDS.)	**Tapscott** reports that exposing rats to 50,000 ppm for 30 minutes resulted in no mortality.[4] (Ex. 1015, Tapscott at

[4] Because no lethality was observed, it can be concluded that the 30-minute LC_{50} of 2-BTP in rats is greater than 50,000 ppm.

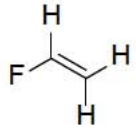
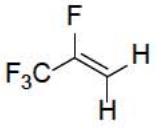
	Butler (Ex. 1138)	**'017 Patent** (Ex. 1001)	**Tapscott** (Ex. 1015)
	1139) reported that the 4-hr LC_{50} value is 315,000 ppm		Table 2.)

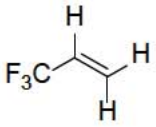
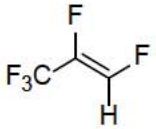
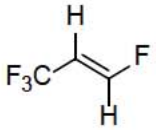
64. Given the above, a toxicologist prior to October 2002 also would have predicted that *trans*-R-1234ze possesses low acute inhalation toxicity. It has four fluorine atoms, a C:F ratio of 0.75, and is structurally similar to both 2-BTP and R-1243zf. Thus, a person of ordinary skill in the art would have reasonably expected R-1234ze to have a low and, specifically, no substantial acute inhalation toxicity.

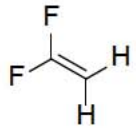
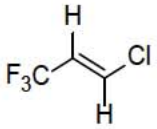
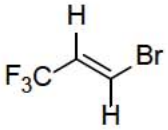
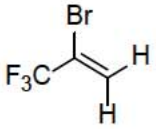
65. Here again, acute toxicity testing confirms that prediction. Honeywell reported that *trans*-R-1234ze has a 4-hour LC_{50} value of at least 200,000 ppm (no mortalities occurred). (Ex. 1145, Third Rusch Decl. ¶¶ 5-6.) In this same Rusch Declaration, Honeywell also reported that R-1233zd, which is identical to *trans*-R-1234ze except that one of the fluorine atoms is replaced with a chlorine atom, has an acute inhalation toxicity of 120,000 ppm for a 4-hour exposure. R-1233zd and *trans*-R-1234ze and their toxicity values confirm the trend that replacing a chlorine with a fluorine will lead to lower acute inhalation toxicity, i.e., >200,000 ppm vs. 120,000 ppm. I note, however, that both of these compounds possess low acute

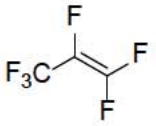
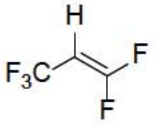
toxicity, and the difference in their LC_{50} values, in practice, has limited toxicological impact.

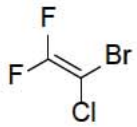
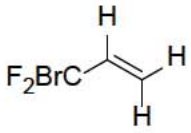
66. In the table below, I have ordered the acute inhalation toxicities of various halogenated compounds from least toxic to most toxic. In this table, I include acute inhalation toxicity values known in 2002 as well as those reported later.

Refrigerant	**Structure**	**Acute Toxicity LC_{50}/ALC***
CH_2=CHF		>800,000 ppm ALC* 4-hr exposure (Ex. 1141, Clayton 1977, Table 1)
R-134a	F_3C-CH_2F	>500,000 ppm* (Ex. 1146, Calm 1996, Table 1)
R-1234yf	 F_3C-CF=CH_2	>400,000 ppm (Ex. 1010, Minor & Spatz at 2)

Refrigerant	Structure	Acute Toxicity LC_{50}/ALC*
R-1243zf	 F_3C-CH=CH_2	Relatively non-toxic* (Ex. 1138, Butler at 2:29-39) 315,000 ppm* (EX. 1139, Dow Corning published results) 430,767 ppm (Ex. 1144, Lifke 2001)
R-1225ye		>250,000 ppm (rats) 100,000-250,000 ppm (mice) (Ex. 1142, Rusch Decl. ¶¶ 3-6)
R-1234ze		>200,000 ppm 4-hr exposure in rats

Refrigerant	Structure	Acute Toxicity LC_{50}/ALC*
	F_3C-CH=CHF	(Ex. 1145, Third Rusch Decl. ¶¶ 5-6)
CF_2=CH_2		128,000 ALC* 4-hr exposure (Ex. 1141, Clayton 1977, Table 1)
R-1233zd F_3C-CH=CHCl		120,000 ppm 4-hr exposure (Ex. 1145, Third Rusch Decl. ¶¶ 7-8)
		>50,000 ppm 30-min exposure (Ex. 1015, Tapscott 2000, Table 2)
2-BTP		>50,000 ppm* 30-min exposure

Refrigerant	Structure	Acute Toxicity LC_{50}/ALC*
	$CF_3CBr=CH_2$	"Even at this extremely high concentration, [2-BTP] showed no lethality." (Ex. 1015, Tapscott at Table 2)
$CF_2=CF_2$ Tetrafluoroethylene (TFE)		40,000 ppm* 4-hr exposure (Ex. 1141, Clayton 1977, Table 1)
$CF_3CF=CF_2$		3,000 ppm 4-hr exposure (Ex. 1141, Clayton 1977, Table 1)
R-1225zc $CF_3CH=CF_2$		<2000 ppm* 4-hr exposure

Refrigerant	Structure	Acute Toxicity LC_{50}/ALC*
		(Ex. 1139, DuPont Published Data)
CF_2=CClBr		250 ppm* 1-hr exposure (Ex. 1140, Clayton 1967 at 230)
CH_2=CHCBrF_2		<50,000 ppm 30-min exposure (Ex. 1015, Tapscott at Table 2)
*Toxicity data known in 2002.		

67. For the foregoing reasons, a person of ordinary skill in the art would have reasonably expected that R-1234yf would have low and no substantial acute toxicity and, from at least a toxicological perspective, it would have been obvious to further develop R-1234yf for use in automotive air-conditioning applications.

IX. Honeywell's Allegedly Unexpected Results Are Exactly What a Person of Ordinary Skill in the Art Would Have Expected

68. During prosecution of the '017 patent, Honeywell submitted toxicity data that it argued demonstrates an unexpectedly better acute toxicity profile for R-1234yf. Honeywell submitted data for R-1225zc showing an LC_{50} of 2,000 ppm. (Ex. 1062, Singh Decl. at 10.) Honeywell argued that "[t]his makes HFO-1225zc approximately **200 times more toxic than HFO-1234yf** based on this measure of toxicity." (Ex. 1050, Office Action dated December 19, 2014, relying on Ex. 1062, Singh Decl. at 10 (emphasis in original).) Based on these data and other chronic toxicity data, Honeywell asserted that "[t]hese results establish that the low toxicity of HFO-1234yf is an important but unexpected advantage of the invention as now claimed." (Ex. 1050 at 10.)

69. I disagree that there was anything unexpected about the difference in acute toxicity between HFO-1234yf and R-1225zc. As discussed in detail above, it was no surprise, and indeed was well-known, by the 1970s that increasing the number of electron withdrawing groups (i.e., fluorine atoms and trifluoromethyl groups) on both ends of a double bond tended to destabilize the double bond and increase the acute toxicity of a compound. (*Supra* at ¶¶ 53-57.) R-1225zc has two fluorine atoms attached to the terminal unsaturated carbon where R-1234yf has two hydrogen atoms. Based on what I have discussed above, prior to 2002, a person of ordinary skill in the art would have expected a compound with five fluorine atoms,

two of which are on the terminal unsaturated carbon atom, to be more toxic than a compound with only four fluorine atoms and with two hydrogens on the terminal unsaturated carbon atom. Thus, in my opinion, Honeywell did not present evidence of unexpected results: the low toxicity of R-1234yf was entirely expected. Instead, Honeywell appeared to simply picked one compound, R-1225zc, and inaccurately offered it as the structurally "closest" analogue. As explained in detail above, a proper analysis would have taken into consideration an aggregate of structurally-related halogen-containing hydrocarbons to establish a hierarchy from which the acute toxicity of R-1234yf (and Inagaki's other exemplary compounds) could have been readily predicted. In my opinion, R-1225zc is not the closest structurally to HFO-1234yf. Instead, R-1243zf and 2-BTP are more closely structurally related to R-1234yf than R-1225zc, and a person of ordinary skill therefore would have expected R-1234yf to have low and no substantial acute toxicity based on the lack of acute inhalation toxicity of these two compounds.

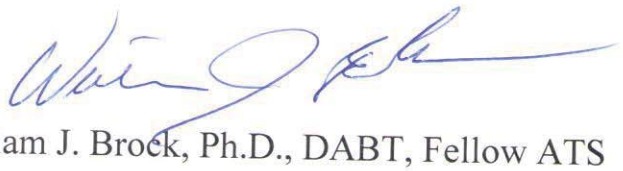
X. CONCLUSION

70. It is my opinion that as of 2002, a person of ordinary skill in the art with the help of his toxicologist colleagues would have predicted with reasonable certainty that R-1234yf would have had no substantial acute toxicity.

71. It is further my opinion that based on the understanding in the art, the low acute toxicity of R-1234yf would not have been surprising or unexpected when compared to R-1225zc. In 2002, based on the structurally similar compounds and toxicity data provided above, a person of ordinary skill in the art with the assistance of his toxicology colleagues would have expected R-1225zc to have a higher degree of acute toxicity because of the higher overall number of fluorine atoms and the two fluorine atoms on the terminal unsaturated carbon.

72. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

February 22, 2016:

By: 

William J. Brock, Ph.D., DABT, Fellow ATS

APPENDIX A

CURRICULUM VITAE

William J. Brock, Ph.D. DABT, Fellow ATS
Brock Scientific Consulting, LLC
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Website: BrockSC.com

PROFESSIONAL EXPERIENCE

Qualifications Summary

About 30 years of experience as a toxicologist, manager and consultant for research and development in the pharmaceutical, consumer product, food, medical device and chemical industries. Experienced in occupational and industrial toxicology; nonclinical safety program study design, conduct, interpretation and reporting; evaluating clinical and product safety data; in training and managing staff; dealing with a wide range of U.S. and foreign regulatory bodies, commercial concerns, and contract research organizations; labeling and other regulatory compliance issues; writing reports, regulatory and toxicology position papers; presentations to regulatory authorities; risk and safety assessments and litigation support.

Brock Scientific Consulting, LLC, Principal, Montgomery Village, MD (2004-present)

- Completed the pharmacology and toxicology section for INDs and NDAs (CTD format) for several pharmaceutical companies for wide range of drug products including for topical, diabetes, anti-infective agents, oncologic, ocular, GI, hormonal, CNS drugs (numerous indications), renal, analgesic, cardiac and gene therapy products
- Worked with clients on developing clinical protocols, investigator brochures, annual reports, PSURs, and case record forms
- Reviewer of early clinical protocols (Phase 1, Phase 2), assisted in establishing first-in-human dose and assisted in the preparation of numerous pharmaceutical product labels
- Served as the primary nonclinical reviewer representing a company in a CARDAC Advisory Committee
- Managing a basic research program to establish a potential mechanism and identify possible genetic and non-genetic biomarkers of patient susceptibility to drug-induced liver injury (DILI)
- Prepared preclinical protocol for juvenile animal model for government research group examining anti-viral drugs and vaccines for use in pediatric populations
- Reviewed safety data and BLA for FDA and Canadian (NDS) regulatory submissions for biologics

- Prepare toxicology reports for vaccines in NHP and rabbits for FDA submission under the Animal Rule
- Prepared numerous toxicity profiles and risk analyses for a variety of substances used in the cosmetic, pharmaceutical, medical device and chemical industries
- Recommended exposure limits (OEL, OEB, etc.) for industrial chemicals, pharmaceuticals, medical device components
- Designed, placed and monitored preclinical programs for clients for inhalation, dermal, oral and intravenous drug products and gene-therapy oncology drug product
- Designed, placed and monitored toxicology programs for clients for chemical products, medical devices, chemical intermediates and food additive materials
- Qualified excipients, impurities and degradants for various prescription and OTC drug products and food substances
- Consulted with large and mid-size consumer product companies on risk evaluation of impurities and testing of new products for the OTC and cosmetic markets
- Prepared food contact notifications and 75-day regulatory notice for dietary supplement
- Prepared exposure assessments of food ingredients for Japanese food ingredient standards
- Created safety assessments for numerous substances used in various industrial sectors (consumer products, chemical, pharmaceutical, etc.) and prepared recommended labeling text and MSDS for those substances
- Provide expert opinions to clients on potential litigation arising from chemical exposures, medical malpractice claims, health effects arising from exposure to molds, indoor air quality claims, ground water contamination, workman's compensation claims, drug and alcohol claims and related traffic accidents and patent infringement claims

Otsuka Pharmaceuticals Rockville MD (2010-2015)

Director of Toxicology. Responsible for all aspects of drug development including regulatory submissions to international regulatory agencies (FDA, EMA, BfRAM, MHRA, PMDA, etc.) and responding to issues raised by the authorities. Managed the nonclinical program in conjunction with colleagues in Japan and reviewed and recommended testing programs for NMEs and biologics. Co-managed basic research program on drug-induced liver injury being conducted at research institutes and universities.

***ENVIRON**, Arlington, VA (2002-2004)*

Senior Science Manager for this international consulting firm providing human and environmental health and risk assessment expertise and regulatory toxicology and litigation support.

- Worked with medical device clients on review of toxicology data and prepared toxicity summary for FDA submission as part of a 510(k)
- Represented medical device client for protocol design and setting dose levels for subchronic and ADME studies
- Worked with a large corporation to prepare a position paper and subsequent manuscript for publication on egress times for fire suppressant agents for the NFPA
- Provided litigation support for toxic tort and workman's compensation claims involving halogenated hydrocarbons, aromatic compounds, glycol ethers, home heating oils and ground water contamination with chlorinated compounds
- Represented a plaintiff in "sick building" syndrome litigation
- Developed PMA toxicity summary for a medical device and medical device components
- Assisted in the development of an epidemiology research program to examine health outcomes for a major technology industry
- Developed testing program and risk assessment strategies for multi-national specialty chemical company
- Prepared a developmental and reproductive toxicity review of an important class of fungicides
- Worked with client on the development of a quantitative logistic regression model to predict cardiac sensitization in military personnel
- Prepared food contact notification for a new substance and submitted it to the FDA/CFSAN
- Assisted a trade association in developing a submission on a food additive for JEFCA
- Assisted developing an investigator IND, clinical protocol and investigator's brochure

***Unilever,** Edgewater, New Jersey* (1999-2002)

Director, SHE Scientific Affairs; Regulatory Toxicologist. Unilever is a worldwide consumer product company for cosmetics, personal care products, home cleaning products and foods. This position was within the Safety and Environmental Assurance Centre (SEAC). The position reported to the Head of SEAC (NA) for administration, and to the Head of Risk Analysis for scientific guidance. Direction for scientific advocacy came from the Senior VP for SEAC.

- Managed emerging regulatory changes, principally in the US, that affected the consumer product and food industries
- Represented Unilever on various external committees, e.g., CTFA, ILSI, being a scientific advocate for the industry
- Expanded a network with various international regulatory agencies and non-government organizations, e.g., FDA, NCTR, NTP, CIR
- Developed regulatory submissions for the Unilever businesses where toxicological data needed to be included
- Developed scientific positions on behalf of Unilever that would result in a strategic business advantage
- Developed an industry consensus on science-based regulatory issues in conjunction with scientists from other organizations
- Provided expertise in the areas of inhalation toxicology, developmental, dermal and ocular toxicology, and interpret regulations that are based on science, e.g., EPA's HPV initiative
- Provided consultation to the junior toxicologists on product safety issues that arise during the routine clearance process of products and ingredients
- Assisted in management responsibilities including operating budget development and guidance to junior personnel in performance evaluations, facility allocation responsibility

E. I. DuPont de Nemours and Company, Wilmington, Delaware (1983-1999)

Worldwide chemical company supplying products into all industrial sectors. The positions held in the last 10 years at DuPont reported to Director of Haskell Laboratory with business responsibility function reporting to the SHE Manager and the Fluoroproducts Division. With re-organization, the Manager of OH reported to the Director of Applied Toxicology

Staff Toxicologist & Manager, Occupational Health, Haskell Laboratory (12/1993-9/1999)

- Functioned as toxicology coordinator that included design, budgeting and interpretation study results; managed an annual toxicology budget of about $2MM and acquired third party contracts (EPA and private industry) of approximately $5MM
- Developed and manage safety and risk assessment programs for new and existing products and coordinate basic and mechanistic research programs on peroxisome proliferation as a mechanism of carcinogenesis
- Coordinator for new chemical notifications including the design and implementation of toxicology programs to support notifications

- Represented science programs to the business to ensure appropriate business decisions were made with respect to product stewardship and protection from potential liability
- Developed regulatory submission for new and existing materials for most of the international regulatory authorities, principally the EPA, FDA, EU, NICNAS and Japanese MHLW, and represent the technical aspects of those submissions to the regulatory authority
- Represented DuPont in various scientific organizations and industry consortia (IPACT, PAFT, CMA, ECETOC, CEFIC); chaired several of these committees
- Led in the preparation of EPA comments on proposed HAPS test rule on HF
- Provided expert testimony on human health in litigation; represented DuPont in approximately 10 cases
- Managed the occupational health programs, industrial hygiene and epidemiology programs

Toxicology Consultant, Technical Services Laboratory (12/1990-12/1993)

- Managed the Product Safety group including conducted compliance audits for TSCA and OSHA as it related to hazard communications, inventory reporting, and agency submissions
- Provided scientific consultation for regulatory compliance and submissions
- Managed the safety and health programs for various product lines including Freons, products used by the consumer product and pharmaceutical industries, e.g., glycolic acid, lactic acid, TiO_2, industrial chemicals used as intermediates for pharmaceuticals, agrichemicals, and other industrial processes

Research Toxicologist, Haskell Laboratory (6/1983-12/1990)

- Functioned as the principal investigator for various toxicology programs that included acute, subchronic, chronic and oncogenicity, developmental and reproduction studies
- Designed and conducted safety assessment programs for pharmaceuticals, commodity chemicals, consumer products and agrichemicals
- Developed and managed toxicology programs for pharmaceuticals, industrial chemicals and agrichemicals
- Represented the data to the sponsor of the studies and to the regulatory agency
- Functioned as the principle investigator for an applied research program examining the role of macromolecular binding of aromatic compounds as a mechanism of carcinogenicity

- Provided expert guidance to various DuPont businesses, assist in the development risk assessment activities for occupational exposures, and develop occupational exposure guidelines

University of Kentucky, *Lexington, Kentucky (*1983)

Post-Doctoral Fellow: *Research Topic: Metabolic Activation of Nicotine-Derived Nitrosamines*
Research Mentor: Dr. Mary Vore, Department of Pharmacology, UK School of Medicine

ACADEMIC TRAINING:

University of Kentucky, *Lexington, Kentucky (*1980-1983)
Post-doctoral Fellowship, metabolism and toxicity of nicotine-derived compounds

University of Kentucky, *Lexington, Kentucky (*1980-1983)
Toxicology Ph.D.

Research Topic: Transport of Organic Anions into Isolated Rat Hepatocytes

University of Kentucky, *Lexington, Kentucky* (1977-1980)
Toxicology M.S.

Research Topic: Behavioral Assessment of Paraquat Toxicity with Single Spatial Alternation and Fixed Ratio Procedures

Geneva College, *Beaver Falls, Pennsylvania (*1972-1976)
Chemistry/Biology B.S.

OTHER PROFESSIONAL EXPERIENCE AAND POSITIONS

University of North Carolina, Chapel Hill, Adjunct Associate Professor, 2014-present

University of Medicine and Dentistry of New Jersey, Adjunct Assistant Professor, 2000-2008

National Toxicology Program, Expert Peer Review Panel for Antimony Trioxide and TRIM VX, 2015-2016.

American Board of Toxicology, Board Member, 2004-2008

American Board of Toxicology, Vice-President, 2006-2007

American Board of Toxicology, President, 2007-2008

Academy of Toxicological Sciences, Board Member, 2006-2011

Academy of Toxicological Sciences, Vice-President, President, 2009-2011

International Pharmaceutical Excipient Council (IPEC), Expert Review Panel, 2008-present

Drug Information Association, Nonclinical Section co-chair, 2008-2011

American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE), Toxicology Standards Committees, 2007-2011; 2011-2014 Chair Toxicology Subcommittee

Society of Toxicology, Member, Program Committee, 2007-2009

Roundtable of Toxicology Consultants, Treasurer, 2003-2010

Society of Toxicology, Member and Chair, Career Resources and Development Committee (CRAD), 2012-2015

Society of Toxicology, Member, Congressional Task Force, 2008-2010

Society of Toxicology, Member, Congressional Task Force, 2008-2010

Society of Toxicology, Nominating Committee, 2001

Society of Toxicology, Member, Finance Committee, 2004-2007

Toxicology Education Foundation Steering Committee, 2004-2005.

American College of Toxicology, Council, 1998-2001

American College of Toxicology, Continuing Education Committee (Chairman), 1998-2001

American College of Toxicology, Membership Committee, 2001-2003

American College of Toxicology, Ad Hoc Program Committee, 2006-2007

American College of Toxicology, Continuing Education Committee, 1997-1998

CTFA, Vice-Chair, Safety and Regulatory Toxicology Committee

ISLI/HESI, Member, Emerging Issues Committee

ILSI/HESI Project, Chairperson, Criteria for Evaluating Epidemiology Issues

CEFIC/EFCTC Toxicology Committee for Fluorocarbon Alternatives and TFE

NRC Committee on Toxicology, Toxicity of Alternatives to Chlorofluorocarbons, 1996

Program for Alternative Fluorocarbon Toxicity Testing (PAFT), Member, 1993-1998

ECETOC, Member, Task Force on Hydrogen Peroxide

CMA, Co-Chair and Member, Panel on HF Medical and Toxicology Task Group

UV Monitoring and Assessment Program, Member, Science Advisory Committee

Hazardous Air Polluting Substances (HAPS) Toxicology Committee, Chairperson, Hydrogen Fluoride

Synthetic Organic Chemical Manufacturing Association (SOCMA), Member, Occupational Safety and Health Committee

Chlorine Institute, Member, HAPS Toxicology Committee for HCl and Chlorine

Institute of Health, NIEHS Study Section, Toxicology Reviewer, 1991

West Chester University, Assistant Professor (interim), Environmental Health Department, 1988-1989

HONORS, PROFESSIONAL SOCIETIES, CERTIFICATIONS

- Diplomate, American Board of Toxicology, 1987–present
- Fellow, Academy of Toxicological Sciences, 2004-present
- Member, Society of Toxicology, 1980 - present
- Member, American College of Toxicology, 1993 - present
- Editorial Board (Associate Editor), International Journal of Toxicology, 2003 – present
- Editorial Board, Journal Applied Toxicology, 1996-2007
- Member, Mid-Atlantic Society of Toxicology, 1985 – 2003
- Member, National Capital Society of Toxicology, 2003 – 2009
- Drug Information Association, 2007-present
- American Association for the Advance of Science, 2008-present

Invited Speaker Presentations:

- American College of Toxicology, Toxicology for Regulatory and Industrial Scientists, 2013, 2014, 2015.
- American College of Toxicology, Advanced Comprehensive Toxicology, 2014, 2015 (course co-organizer).
- Association for Research in Vision and Ophthalmology, Good Laboratory Practices Regulations in a Toxicology Environment, May 2014.
- Toxicology for Regulatory Scientists, American College of Toxicology, 2012-present.

- Role of the Study Director in Nonclinical Studies, Course Organizer and Speaker, 2012, Bangalore, India; 2010, Beijing, China.
- Drug Development: An Industry Perspective, FAES Program, NIH, 2014, 2015.
- DIA Annual Meeting, Nonclinical and Clinical Strategies in First-in-Human of Large and Small Molecules, Chicago, 2011
- University of Kentucky, Graduate Center for Toxicology. Drug Development and Nonclinical Requirements, 2008.
- Invited speaker to the Chinese National Standards committee meeting on the topic of fluorocarbon toxicology and international classification (2007).
- NRC Committee on Toxicology, Invited speaker, Toxicity of Alternatives to Chlorofluorocarbons – HFC-23 and HFC-236fa, 1998.
- Conference on CFC Alternatives, Invited Speaker, Toxicology of Alternatives to Chlorofluorocarbons (CFC's*)*, 1992
- World-wide Producers of Hydrogen Peroxide, Presentation, Toxicology of Hydrogen Peroxide, Kyoto, Japan, 1990
- Fish and Wildlife Services, Partnership in Drug Approval, Genotoxicity in Safety Assessment and Risk Assessment Methods in Establishing the ADI (2010)
- National Library of Medicine, National Institute of Health, Expert Panel on HSDB Needs Assessment. November 8, 2011

ABSTRACTS:

Woodhead, J.L., Brock, W., Roth, S., Brouwer, K.L.R., Siler, S.Q., Church, R.C., Watkins, P.B., Shoaf, S.E., Howell, B.A. and Shoda, L.K.M. 2015. Quantitative Systems Modeling Provides Biological Plausibility For Potential Mechanisms Of Tolvaptan-Induced Hepatotoxicity. Internat. Soc. Pharmacometrics, 6th Annual Meeting, October 2015.

Mosedale, M., Eaddy, J.S., Trask, O.J. Jr., Holman, N.S., Wolf, K.K. LeCluyse, E. Brock, W.J. Roth, S.E. and Watkins, P.B. 2016. miR-122 Release in Exosomes Accompanies Tolvaptan-Induced Mitochondrial Dysfunction, Oxidative Stress and Apoptosis in a Micropatterned Primary Human Hepatocyte Coculture Model. The Toxicologist, Supplement to Toxicological Sciences, 145 (1), Abstract XXX.

Lu, Y., Slizgi, J., Brock, W.J., Pan, M., and Brouwer, K.L. 2015. Inhibition of BSEP- and NTCP-Mediated Taurocholate Transport by Tolvaptan and Metabolites. The Toxicologist, Supplement to Toxicological Sciences, 144 (1), Abstract 715.

Brouwer, K.R., Jackson, J.P., Freeman, K.M., Hubert, C., St Claire, R., Pan, M., and Brock, W.J. 2015. Effect of Tolvaptan on the Hepatobiliary Disposition of Bile Acids in Human B-CLEAR Hepatocytes. The Toxicologist, Supplement to Toxicological Sciences, 144 (1), Abstract 716.

Mosedale, M., Wiltshire, T., Eaddy, J.S., Brock, W.J., Roth, S., Dodd, D.E., Corty, R.W., Xie, Y., Valadar, W. and Watkins, P.B. 2015. Candidate Risk Factors for Tolvaptan-Induced Liver Injury Are Identified Using a Collaborative Cross Approach. The Toxicologist, Supplement to Toxicological Sciences, 144 (1), Abstract 717.

Y. Shimomura, Y. Ito, J. Kino, R. Kawata, K. Morishita and W. J. Brock. 2015. Pathological and Clinical Pathological Detection of Age-Related Liver and Kidney Malfunction in the Polycystic Kidney (PCK) Rat: An Animal Model of Polycystic Kidney Disease. The Toxicologist, Supplement to Toxicological Sciences, 144 (1), Abstract 1828.

Levine, T.E. and Brock, W.J. 2015. Challenges in the Life Cycle of a Toxicologist. The Toxicologist, Supplement to Toxicological Sciences, 144 (1), Abstract 814.

Mosedale, M., Brock, W.J., Roth, S. Eaddy, J.S., Wiltshire, T., Trask, O.J., Corty, R.W., Xie, Y., Valadar, W. and Watkins, P.B. 2015. Personalized DILI risk management: The tolvaptan initiative. FDA/Pharma/Critical Path Annual DILI Conference, College Park, MD.

Wiltshire, T., Eaddy, J.S., Brock, W.J., Roth, S., Dodd, D.E. Watkins, P.B., and Mosedale, M. 2014. Mouse models for idiosyncratic tolvaptan-induced liver injury using a Collaborative Cross Mouse. International Mammalian Genome Society, Bar Harbor, ME.

Brock, W.J. and Genter, M.B. 2014. Scientific ethics in research and publications. Toxicologist, 138: 726

Brock, W.J. and Faqi, A. 2010. Ovarian Toxicity: Current concepts in toxicology, pathology and mechanisms. Toxicologist, 114: 25.

Brock, W.J., Schroeder, R., MacKnight, C., VanSteenHouse, J. and Nyberg, J. 2010. Repeat dose oral and reproductive toxicity of the chlorinated flame retardant Dechlorane Plus. Toxicologist, 114: 1173

Brock, W.J. and Faqi, A. 2009. Dioxin, Forty Years of Science: Are We Any Closer to Assessing Potential Risk? Toxicologist 108.

Brock, W. J., Trochimowicz, H. J., Cisneros, M. and Rusch, G. M. (2003). Application of experimental cardiac sensitization results in physiologically-based pharmacokinetic models. The Toxicologist, 72: 303 (abstract 1474).

Bamberger, J.R., Scott, R.S., Hansen, J.F., Ladics, G.S., Brock, W.J., Elliott, G.S., Hurtt, M.E. and Swanson, M.S. (2000). Ninety Day Inhalation Toxicity Study of HCC-230fa in Rats. The Toxicologist, Abstracts, 1707:364.

Kelly, D.P., Hansen, J., Brock, W., Barter, J. and Burleigh-Flayer, H. (2000). Acute Inhalation Toxicity of *Cis and Trans* Isomers of 1,2-Dichloroethylene in Rats. The Toxicologist, 81:17.

O'Neill, A. J., Baric, R. J., Everds, N. E., Frame, S. R., O'Connor, J. R., and Brock, W. J. (1999). 90-Day Inhalation Toxicity of 1,1-Difluoro-1,2,2-Trichloroethane (HCFC-122) in Rats. The Toxicologist, 48:1318.

Brock, W. J., Wun-Kim, K, Cox, L. R., Gerber, K. M. and Bentley, K. S. (1999). Genetic Toxicity Testing of HFPO Trimer and HFPO Trimer Ammonium Salt. The Toxicologist, 48: 583.

Kelly, D. P., Ross, P. W., Brock, W. J., Barter, J. A., Burleigh-Flaver, H. and Lieder, P. H. (1999). Ninety-Day Inhalation Toxicity of Trans-1,2-Dichloroethylene in Rats. The Toxicologist, 48: 559.

Bamberger, J. R., Lavoie, D. A., Elliott, G. S., Chiu, T. and Brock, W. J. (1999). Subacute Inhalation Toxicity of Perfluoroethyl Vinyl Ether (PEVE) in Rats. The Toxicologist, 48:143.

Weiner, M. L., Freeman, C., Trochimowicz, H., Brock, W., De Gerlache, J., Malinverno, G., Mayr, W. and Regnier, J. F. (1998). A 13-Week Drinking Water Study With 6-Week Recovery Period in Catalase-Deficient Mice With Hydrogen Peroxide. INTOX Meeting, Paris.

Kennedy, G. L., Keller, D. A., Biegel, L. B. and Brock, W. J. (1998). Repeated-Dose Toxicity of Fluorinated Acids in Rats. The Toxicologist, 42:1828.

Keller, D. A., Hurtt, M. E., Brock, W. J. and Slauter, R. E. (1998). Pharmacokinetics and Effects of HCFC-123 on Hepatic Biochemistry and Lactational Parameters in Rhesus Monkeys. The Toxicologist, 42:1269.

Malinverno, G., W. Brock and S. Magda. (1997). Reproduction Studies with HCFC Alternatives. Pharmacology and Toxicology, 80 (Suppl. III):139.

Brock, W. J. and H. J. Trochimowicz. (1997). Use of Acute Inhalation Toxicity Data in Setting Emergency Exposure Limits. Pharmacology & Toxicology, 80 (Suppl. III):117.

Valentine, R., Keller, D. A., Cook, J. C., Biegel, L. G., Elliott, G. S., Stone, T. W., Munley, S. M., Bentley, K. S., and Brock W. J., and Briggs, G. B. (1996). Toxicologic profile of the alternative refrigerant, HFC-236FA. The Toxicologist, 30:1489.

Brock, W. J., Kelly, D. P., Stadler, J. C., Elliott, G. S., Slone, T. W., Munley, S. M., Bentley, K. S., and Briggs, G. B. (1996). Toxicological evaluations of the CFC alternative HFC-236EA. The Toxicologist, 30:1482

Brock, W. J., Kelly, D. P., Stadler, J. C., Elliott, G. S., Slone, T. W., Munley, S. M., Bentley, K. S., and Briggs, G. B. (1996). Toxicological evaluations of the CFC alternative HFC-236EA. The Toxicologist, 30:1482

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Kelly, D. P., Gerber, K. M., Slone, T. W. and Brock, W. J. (1996). Two-week inhalation rat study and *in vivo/in vitro* mutagenicity studies with perfluoropentene-2. The Toxicologist, 30:99

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Brock, W.J. and Trochimowicz, H.J. (1993). Review of the toxicology of the CFC alternatives. Amer. Chem. Soc.

Brock, W.J. and Trochimowicz, H.J. (1995). Comparative toxicology of the CFC and HFC alternatives. The Toxicologist, 15:191.

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Brock, W. J., Hundley, S. G., and Lieder, P. H. (1990). Macromolecular binding and tissue distribution of o- and p-toluidine. The Toxicologist, 6.

Hughes, M. F., Brock, W. J., and Vore M. (1984). Covalent binding of 14C-N-nitrosonornicotine (NNN) mediated by rat liver microsomes. The Toxicologist, 4:531.

Hughes, M. F., Brock, W. J., Durham, S. and Vore, M. (1983). Effect of pregnancy on the uptake of estrone, morphine and taurocholate in isolated rat hepatocytes. The Pharmacologist, 25:49.

Brock, W. J., Coupal, J. J., Shih, W. T., Vore, M. and DeLand, F. H. (1983). The uptake of hepatobiliary imaging agents into isolated rat hepatocytes: The effect of bile acids and bilirubin. The Pharmacologist, 25:50.

Brock, W. J. and Vore, M. (1983). The uptake of organic anions into hepatocytes isolated from male, female and estradiol-17β treated rats. Fed. Proc., 42:491.

Brock, W. J. and Vore, M. (1982). Effect of pregnancy, estradiol-17β, and 2,3,7,8-tetrachlorodibenzo-p-dioxin on the uptake of organic anions in isolated rat hepatocytes. The Pharmacologist, 24:98.

Brock, W. J., Montgomery, C. and Vore, M. (1981). Elimination of [14C]-morphine in the isolated perfused liver of pregnant, estradiol-17β, (E2) treated, and nonpregnant (NP) rats. The Toxicologist, 1:87.

Brock, W. J. and Vore, M. (1980). Effect of pregnancy, estradiol, and 2,3,7,8-tetrachlorodibenzo-p-dioxin on hepatic estrone and morphine glucuronyltransferase activity. The Pharmacologist, 22:242.

Brock, W. J. and Dougherty, J. A. (1980). Behavioral effects of paraquat. Soc. Neuroscience Abstracts, 6:593.

Brock, W. J. and Dougherty, J. A. (1979). Effect of d-amphetamine and paraquat on single spatial alternation performance. Toxicol. Appl. Pharmacol., 48:A51.

PUBLICATIONS

Mosedale M, Wiltshire T, Corty RW, Eaddy JS, Kim Y, Xie Y, Roth SE, Brock WJ and Watkins PB. 2015. Candidate risk factors for tolvaptan-induced liver injury are identified using a collaborative cross approach. In preparation.

Slizgi, J., Lu, Y., Brouwer, K., St. Claire, R., Pan, M., Brock, W.J., and Brouwer, K.L. 2015. Inhibition of Human Bile Acid transporters by Tolvaptan and Metabolites. Toxicol. Sci. ePub. . doi: 10.1093/toxsci/kfv231.

Shimomura, Y. Brock, W.J., Ito, Y. and Morishita, K. 2015. Age-Related Alterations in Blood Biochemical Characterization of Hepatorenal Function in the PCK Rat: A Model of Polycystic Kidney Disease. Internat. J. Toxicol. In press.

Brock, W.J. 2014. Strengthening the peer review process for the International Journal of Toxicology: Editorial. 33: 351-352.

Hildebrandt, K., Steines, S.A. and Brock, W.J. 2014. Need for dedicated equipment? Manufacturing of anti-neoplastics and other hazardous substances. Pharm. Ind. 76: 78-724.

Brock, W.J., Somps, C.J., Render, J., Jamison, J. and Torti, V. 2013. Ocular toxicity from systemically administered xenobiotics: A symposium review. Int. J. Toxicol. 32: 171-188.

Brock, W.J. and Bell, T.J. 2012. Genotoxicity of benzocaine. Int. J. Toxicol. 31: 222-227.

SIAC's Combine for Strategic First-in-Human Dosing Workshop. 2011. DIA Global Forum, 3(3): 95-97.

Brock, W.J., Schroeder, R., MacKnight, C., VanSteenHouse, J. and Nyberg, J. 2010. Repeat dose oral and reproductive toxicity of the chlorinated flame retardant Dechlorane Plus. Int. J. Toxicol. 29: 582-593.

DeMerlis, C. Goldring, J., Velagaleti, R. and Brock, W. 2009. Regulatory Update: The IPEC Novel Excipient Safety Evaluation Procedure. PharmTech. 33: 72-82.

Brock, W.J., Woolley, A.P.H. Woolley, and Sugimoto, T. 2009. Certification in Toxicology: An International Perspective of Risk:Benefit. Internat. J. Toxicol. 28: 147-150.

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Brock, W. J., Rodricks, J. V., Rulis, A., Dellarco, V., Gray, G. and Lane, R. (2003) Food safety: Risk assessment methodology and decision making criteria. Int. J. Toxicol., 22: 435-451.

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Brock, W. J., Trochimowicz, H. J. and Rusch, G. M. (2003) Cardiac sensitization: Methods and interpretation for risk assessment: A Review. Reg. Toxicol. Pharmacol. 38:78-90.

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Cattie, S.L. Filliben, T. A. and Brock, W.J. (2000). Acute Toxicity Studies With EVE Carbamate. Int. J. Toxicol., Acute Toxicity Supplement, 19:361.

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Keller, D. A., Lieder, P. H., Brock, W. J. and Cook, J. (1998). 1,1,1-Trifluoro-2,2-dichloroethane (HCFC-123) and 1,1,1-Trifluoro-2-bromo-2-chloroethane (Halothane) Cause Similar Biochemical Effects in Rats Exposed by Inhalation for Five Days. Drug Chem. Toxicol., 21:405-415.

Brock, W. J. (1998). Safety and Development of Hydrofluorocarbons. In: Abstracts of the Workshops on Toxicity of Alternatives to Chlorofluorocarbons, R. Snyder, K. S. Bakshi and B. M. Wagner, eds. Inhal. Toxicol. 9:775-810.

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Malley, L. A., Frame, S. R., Elliott, G. S., Bentley, K. S., Brock, W. J., Trochimowicz, H. J., and Rusch, G. M. (1998). Chronic Toxicity, Oncogenicity, and Mutagenicity Studies with Chlorotetrafluoroethane (HCFC-124). Drug Chem Toxicol., 21(4):417-427.

Sarver, J. W., Montgomery, R. R., and Brock, W. J. (1996). Dermal irritation and corrosion studies with glycolic acid. J. Amer. Coll. Toxicol., 15 (Suppl. 1).

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Sarver, J. W., Finlay, C., Brock, W. J. and Malek, D. E. (1996). Eye irritation and skin corrosion evaluations with hydrogen peroxide. J. Amer. Coll. Toxicol., 15(Suppl. 1).

Brock, W. J., Trochimowicz, Farr, C.H., Millischer, R.J. and Rusch, G.M. (1996). Acute, subchronic, and developmental toxicity and genotoxicity of 1,1,1-Trifluoroethane (HFC-143a). Fund. Appl. Toxicol., 31:200-209.

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Brock, W. J., Hundley, S. G., Lieder, P. H. (1990). Macromolecular binding and tissue distribution of o- and p-toluidine. Toxicol. Lett. 54:317-32

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APPENDIX B

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MATERIALS CONSIDERED—WILLIAM J. BROCK, PH.D., DABT, FELLOW ATS

Exhibit 1001	U.S. Patent No. 9,157,017 to Singh et al.
Exhibit 1010	B. Minor & M. Spatz, *HFO-1234yf Low GWP Refrigerant Update*, Int'l Refrigeration & Air Conditioning Conf., Paper 937 (2008)
Exhibit 1012	Japanese Patent App. Publication No. JP H4-110388 to Inagaki et al., dated April 10, 1992 (English Translation)
Exhibit 1015	Robert E. Tapscott, *Tropodegradable Fluorocarbon Replacements for Ozone-Depleting and Global-Warming Chemicals*, 101 J. Fluorine Chemistry 209 (2000)
Exhibit 1050	Amendment dated December 19, 2014 in U.S. Patent Application No. 14/225,588, filed March 26, 2014
Exhibit 1062	Declaration of Rajiv Ratna Singh filed submitted for Reexam Control No. 95/002,030 (dated December 24, 2012); and filed in the Prosecution History of U.S. Patent No. 9,157,017 on August 29, 2014
Exhibit 1077	29 C.F.R. § 1910.1200 app. A (2002)
Exhibit 1112	James M. Calm & David A. Didion, *Trade-Offs in Refrigerant Selections: Past, Present, and Future*, ASHRAE/NIST Refrigerants Conf. (Oct. 6-7, 1997)
Exhibit 1138	U.S. Patent No. 3,884,828 to Butler
Exhibit 1139	Dow Corning, Acute Vapor Inhalation Toxicity of TX-52 (Submitted to EPA Dec. 17, 1991)
Exhibit 1140	J. Wesley Clayton, Jr., *Fluorocarbon Toxicity and Biological Action*, 1 Fluorine Chemistry Revs. 197 (1967)
Exhibit 1141	J. Wesley Clayton, *Toxicology of the Fluoroalkenes: Review and Research Needs*, 21 Env't Health Persp. 255 (1977)
Exhibit 1142	Declaration of Dr. George Rusch submitted during prosecution of U.S. Patent Application No. 10/837,525 (dated April 25, 2007); and filed in the Prosecution History of U.S. Patent No. 9,157,017 on August 29, 2014
Exhibit 1143	Honeywell, *Safety Data Sheet: R-1234yf* (Revised June 17, 2014)
Exhibit 1144	Joseph Lifke et al., *Tropodegradable Bromocarbon Extinguishants* (May 2001)
Exhibit 1145	Third Declaration of George Rusch, Ph.D. in U.S. Patent

	Application No. 12/412,342, dated July 28, 2010
Exhibit 1146	J.M. Calm. *The Toxicity of Refrigerants*, Int'l Refrigeration & Air Conditioning Conf., Paper 317 (1996)
Exhibit 1148	Letters from A. Michael Kaplan, Dir.-Regulatory Affairs, DuPont, to Office of Pollution Prevention and Toxics, Envt'l Prot. Agency (2000)
Exhibit 1154	Am. Nat'l Standards Inst., ASHRAE Standard 34-2004: Designation and Safety Classification of Refrigerants (2004)