CARDIAC SENSITIZATION: METHODS DEVELOPMENT AND UNDERSTANDING THE HAZARD AND POTENTIAL RISK

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Since the early 1900s, it has been known that the inhalation of volatile anesthetic agents like cyclopro-pane and chloroform can make the mammalian heart abnormally sensitive to adrenaline, resulting in cardiac arrhythmia and possible death. This "increased sensitivity of the heart to adrenaline brought about by exposure to high concentrations of certain organic chemicals" is referred to as cardiac sensitiza-tion. Since that time, many halocarbons and hydrocarbons have been shown to induce cardiac sensitization.

In the late 1960s, we began to hear of deaths related to the "sniffing" of chlorofluorocarbon (CFC) aerosol propellants. "Sniffing," incidentally, is really a misnomer since the practice involved the deliberate, deep inhalation of highly concentrated vapors from a balloon or plastic bag in order to achieve an "anesthetic high." In 1970, our laboratory was first to present experimental evidence that fluorocarbon propellants, like many other halocarbons and hydrocarbons, were capable of inducing cardiac sensitization and that this phenomenon was the probable cause of death in the aerosol "sniffing" cases.

In our 17-min protocol, a conscious beagle dog, fitted with a flow-through mask, was exposed to various gaseous concentrations of the test compound in air, given intravenous epinephrine injections before and during exposure, and ECG response was monitored continuously. For the first 2 min of the experiment, the dog was allowed to breathe air alone and then a control injection of epinephrine (0.008 mg/kg) was administered over a 9-sec time interval. From 2 to 12 min, the dog was then allowed to breathe a specific concentration of the compound-air mixture. **After** a 5-min exposure to the compound-air mixture, a challenge injection of epinephrine (same dose as earlier) was given. If the compound at the specified concentration were a cardiac sensitizer, a life-threatening arrhythmia would be seen on the ECG. After the 10-min exposure to the compound, the dog was allowed to breathe air alone for another 5 min (min 12 to min 17 of the test protocol).

Since epinephrine alone can cause ventricular fibrillation when injected in sufficient quantity, it was necessary to use a smaller dose to look for possible synergistic effects. The dose of epinephrine used in our screening experiments was 0.008 mg/kg, which is similar to that used by other investigators. This dose, given intravenously in 1 ml of saline over a 9-sec period, would provide a dose of about 0.050 mg/kg/min. The latter dose is probably about 10x the dose calculated to be present in man (0.005 mg/kg/min) during times of stress. In addition, our dose of 0.008 mg/kg given in 9 sec was the highest concentration at which no serious arrhythmia was ever induced (from the epinephrine alone) based on experimental trials on hundreds of beagle dogs.

To better extrapolate to the human situation, dogs were exposed to potential sensitizing agents and made to generate their own adrenaline. In the first of these experiments, conscious beagle dogs were exposed by inhalation to the agent (80% compound, 20% oxygen) for approximately

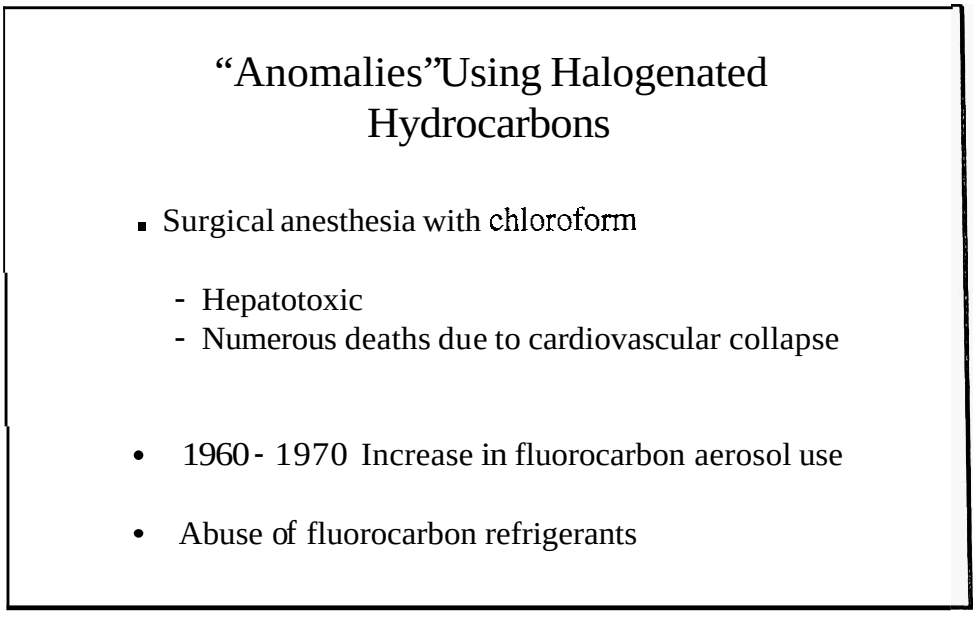
30 sec and then frightened (tape recording of horn blasts, sirens, lion roars, etc.). If the compound were a cardiac sensitizing agent, evidence of a serious arrhythmia would be seen on the electrocardiogram.

In a second set of studies, dogs were exposed to specific inhaled concentrations of the test agent for approximately 20 min while they ran on a treadmill (–500 ft/min.) to generate their own adrenaline. This exercise rate results in about a five-fold increase in circulating adrenaline. If the test compound at a specific concentration was a sensitizing agent, a life-threatening arrhythmia (multiple ventricular beats, for example) would be seen on the electrocardiogram.

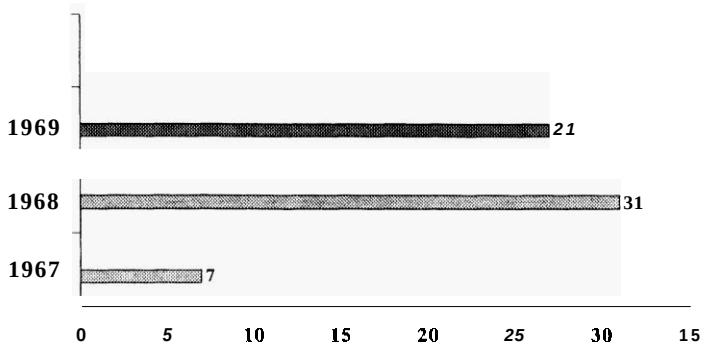
One other experiment relative to cardiac sensitization is worth mentioning. Dogs with experimentally induced myocardial infarction were tested to determine whether this type of common heart condition might significantly lower the threshold for cardiac sensitization in our screening test using exogenous epinephrine. There was no greater potential for cardiac sensitization among dogs having recovered from myocardial infarction as compared to dogs with normal healthy hearts.

There is much evidence indicating that cardiac sensitization is not simply an interesting laboratory finding, but that it can and has occurred in humans during times of stress while being exposed to certain, unsubstituted and halogenated hydrocarbons. The results of the screening studies and endogenous epinephrine experiments indicate that all of the fluorocarbons tested to date are capable of sensitizing the mammalian heart to epinephrine, resulting in serious cardiac arrhythmias. The "fright" and treadmill studies are particularly significant in that cardiac arrhythmias were induced without the administration of exogenous epinephrdne.

The screening protocol we developed is considered to provide a sensitive and rigorous screening test for determining the cardiac sensitization potential of a compound and, as such, is intended mainly to identify and generally rank compounds. For example, CFC-11 sensitizes dogs at ≥ 0.5% (v/v) and is considered a "strong sensitizer" (0.1-2.5%). CFC-12 sensitizes at ≥ 5.0% and can be labeled a "moderate sensitizer" (2.5-7.5%), while CFC-115, on the other hand, sensitizes at ≥ 15.0% and would be considered a "weak sensitizer."



Aerosol **Sniffing** Deaths



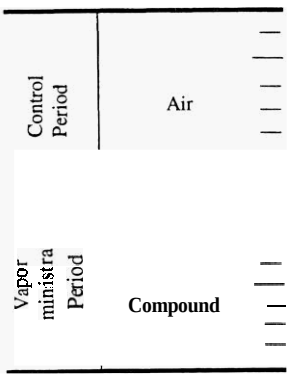
Possible Mechanisms of Sudden Death in "Sniffing" Cases

- Anoxia
- Narcosis
- Laryngeal Spasms
- Cardiac Sensitization

Cardiac Sensitization

Increased sensitivity of the heart to adrenaline brought about by exposure to high concentrations of certain organic compounds.

Protocol for Experimental Screening Study for Cardiac Sensitization in Dogs



0 min.	Start
2 min.	Administer epinephrine intravenously
7 min.	Administer compound
12 min.	Administer epinephrine (challenge injection) of same dose as above
17 min.	Stop compound administration; end experiment

Factors Necessary for Cardiac Sensitization to Occur

1. Exposure to high concentration of hydrocarbon vapor or gas.

2. High circulating level of adrenaline in the body (brought on by anxiety or exertion).

Cardiac Sensitization: Results of Screening Studies in Dogs

Fluorocarbons	Exposure Concentrations	# Dogs Sensitized
CFC-11	1000	0/12
	5000	1/12
	10,000	5/12
HCFC-22	25,000	0/12
	50,000	2/12
Halon 1301	50,000	0/62
	75,000	1/18
	100,000	8/69
	150,000	2/7
	200,000	8/13
HCFC-123	10,000	0/3
	20,000	4/6
	40,000	3/3
HFC-236fa	50,000	0/6
	100,000	0/6
	150,000	2/6
	200,000	2/5

Endogenous Adrenaline Studies

Experiment 1 (Fright):

- Exposed groups (n with 12/compound) of dogs to 80% fluorocarbon
- Exposure for 30 seconds
- SO% compound supplemented with O_2
- At end of 30 seconds, "frighten" dog with noise—horn blasts, siren, etc.
- Record EKG

Experiment 2 (Flight):

- Dog ran on treadmill (~500 ft/min)
- Expose to various concentrations of fluorocarbon
- Record EKG

Endogenous Adrenaline Studies
"Fright Studies"

Fluorocarbon	# of Dogs Sensitized
CFC-11	2/12
CFC-12	0/12
HCFC-114	1/12
HCFC-142b	
+Noise	5112
- Noise	1112
Noise alone	016

Endogenous Adrenaline Studies
"Flight Studies"

Fluorocarbon	Exposure Concentration	#of Dogs Sensitized
CFC-12	*50,000* ppm	*0*/6
	75,000 ppm	*0*/6
	100,000 ppm	0/6
CFC-I 1	5,000 ppm	0/8
	7,500 ppm	0/8
	10,000 ppm	0/8

Is There Increased Risk to Cardiac Sensitization With Prior Cardiac Damage?

- Helical wire surgically inserted into coronary artery
- Induced myocardial infarction ("heart attack")
- About 5 weeks post-operatively, exposed to fluorocarbon
- Monitored EKG for cardiac sensitization

Comparison of "Cardiac" and Normal Dogs for Cardiac Sensitization

Fluorocarbon	Exposure Concentration	#of Dogs Sensitized Cardiac	Normal
CFC-I1	1000 ppm	0/12	0/12
	5000 ppm	1/12	2/24
	10,000 ppm	6/12	5/12
Halon 1301	50,000 ppm	0/10	0/62
	75,000 ppm	0/10	1/18
	100,000 ppm	2/10	8/69

Blood Concentrations Associated With Cardiac Sensitization in Dogs

CFC	Exposure Conc (ppm)	No. of Dogs Sensitized/Tested	Blood Concentration µg/ml Arterial	Venous
11	1000	0/12	10.9	6.6
	5000	1/12	28.6	19.7
	10,000	5/12	53.2	37.2
12	1000	N.D.	1.0	1.9
	25,000	0/12	N.D.	N.D.
	50,000	5/12	35.3	22.8
	100,000	N.D.	46.3	39.8
113	1000	N.D.	2.6	1.5
	2500	0/12	N.D.	N.D.
	5000	10/29	12.5	4.9
	10,000	3/4	18.0	12.1
114	1000	N.D.	0.4	0.2
	25.m	1/12	13.8	7.2
	50,000	7112	23.6	10.0
115	100,000	N.D.	2.8	1.9
	150,000	1/13	5.8	3.9
	2w.m	4/12	11.4	5.9

Animal Models for Cardiac Sensitization

- Rat
- Mouse
- Monkey
- Guinea Pig
- Dog

Conclusions

- Hazard
  - Cardiac Sensitization
- Risk
  - Exposure to **2-4** fold greater concentrations
  - Increased adrenaline blood levels
  - **No** apparent risk to pre-existing cardiac conditions