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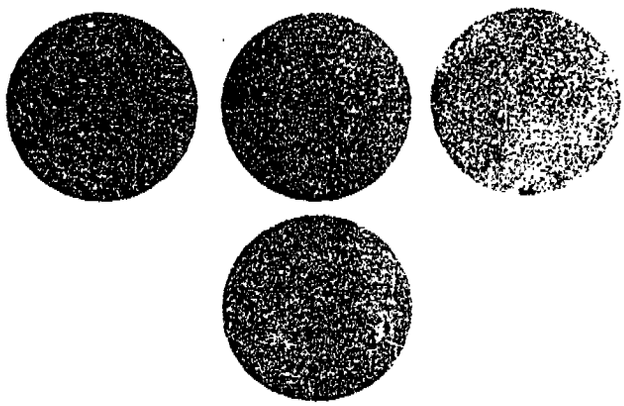



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# TOXICITY OF AEROSOL PROPELLANTS IN THE RESPIRATORY AND CIRCULATORY SYSTEMS

## VIII. RESPIRATION AND CIRCULATION IN PRIMATES*

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SUMMARY

The low-pressure propellants influence predominantly the circulation, whereas the high pressure propellants affect the respiration in anesthetized monkeys. There are four groups according to the level of toxicity: *Class 1*, low-pressure propellants of high toxicity that cause tachycardia and hypotension; *Class 2*, low-pressure propellants of intermediate toxicity that influence either circulation or respiration or both; *Class 3*, high-pressure propellants of intermediate toxicity that cause bronchoconstriction, and *Class 4*, high-pressure propellants of low toxicity that do not influence respiration or circulation even when inhaled at levels of up to 20% concentration.

## INTRODUCTION

So far in this series of investigations the effects of 8 propellants have been studied in two animal species: 7 in the rat [7] and 3 in the mouse [4]. 3 of these propellants cause bronchoconstriction and respiratory depression, and 5 influence only bronchomotor tone or respiration but not both. Since there are 15 propellants that are being compared, the respiratory profile is still unknown for 7. For the sake of completeness, all 15 are presently compared in the monkey with measurements of respiratory minute volume, pulmonary resistance and pulmonary compliance. The aortic blood pressure and heart rate are also recorded to arrive at a general statement as to the comparative sensitivity of the respiratory and circulatory systems.

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This is the third comparison of all 15 propellants which has not been hitherto attempted. The first one was for the detection of proarrhythmic activity in mice [1] and the second concerned depression of cardiac contractility in the monkey [3]. The results were used to classify the propellants on the basis of their potency and the nature of the cardiotoxicity involved. The differentiation of the propellants on the basis of their vapor pressure was completely ignored. However, since recent events have prompted the necessity to discard some widely used propellants, the choice of substitutes would be facilitated if the classification would separate the high-pressure propellants from the low-pressure ones. The differentiation between the two is based on the vapor pressure and boiling point: propellants with vapor pressure less than 31 psig and boiling point above −11° are *low-pressure* ones and those with a higher vapor pressure and lower boiling point are characterized as *high-pressure*. The classification which is proposed below takes into consideration the pressure as well as the level of toxicity affecting the respiratory and circulatory systems.

## EXPERIMENTAL MATERIALS AND METHODS

### *Propellants administered by inhalation*

The fifteen compounds are grouped according to their vapor pressure and boiling point into high- and low-pressure propellants. All but five are fluorinated and are identified by fluorocarbon (FC) numbers which denote the position of the fluorine and chlorine substitution. The chemical structures of the compounds arranged in the decreasing order of the boiling point at one atmosphere are as follows:

| | Boiling point °C | Vapor pressure psig at 20°C |
|---|---|---|
| *Low-pressure propellants* | | |
| Trichloroethane | 74.1 | −12.5 |
| FC 113; Trichlorotrifluoroethane | 47.6 | − 9.2 |
| Methylene chloride | 40.1 | − 7.3 |
| FC 11; Trichlorofluoromethane | 23.8 | − 1.3 |
| FC 21; Dichloromonofluoromethane | 8.9 | 8.4 |
| FC 114; Dichlorotetrafluoroethane | 3.8 | 12.9 |
| FC C-318; Octafluorocyclobutane | − 5.8 | 25.4 |
| FC 142b; Monochlorodifluoroethane | −10.0 | 29.1 |
| Isobutane | −10.2 | 30.0 |
| *High-pressure propellants* | | |
| Vinyl chloride | −13.9 | 31.5 |
| FC 152a; Difluoroethane | −24.7 | 63.0 |
| FC 12; Dichlorodifluoromethane | −29.8 | 70.2 |
| FC 115; Chloropentafluoroethane | −38.7 | 103.0 |
| FC 22; Monochlorodifluoromethane | −40.8 | 121.4 |
| Propane | −42.2 | 130.3 |

With the exception of FC 11, all of the compounds examined exist in the vapor or gaseous phase at normal ambient temperature and pressure and were therefore stored in pressure cylinders. The desired concentrations were attained by delivering a metered volume of the gas from the cylinder and diluting it with a known volume of air. The vapor of fluorocarbon 11 (boiling point 23.8°) was generated by heating the compound in a water bath. The following concentrations were used: 2.5, 5, 10 and 20% of the vapor or gas in air. The mixture was administered for 5 min alternately with room air for 15 min.

*Measurement of bronchopulmonary function*

Rhesus monkeys (*Macaca mulatta*), weighing from 1.8 to 2.7 kg, were anesthetized by intravenous injection of 30 mg/kg sodium pentobarbital and the trachea was cannulated. Lead II electrocardiogram and femoral arterial blood pressure were recorded. Pulmonary resistance and compliance were estimated from measurements of tracheal air flow and transpulmonary pressure. The tracheal cannula was connected to a mesh screen Fleisch pneumotachograph with a heating unit to maintain inspired air at a constant temperature, and the pressure difference across the screen was measured by a differential pressure transducer. The signal from the transducer corresponding to air flow was in turn integrated and recorded as tidal volume. Respiratory minute volume was obtained by means of an integrating preamplifier which converted the flow measurements into volume.

The pressure difference between the trachea and the intrapleural space was measured with a second differential transducer. To determine pulmonary resistance, the flow and pressure signals were displayed simultaneously on both axes of the oscilloscope screen to show a Pressure-Flow loop. Subsequently an amount of pressure proportional to volume was subtracted, so that the loop was closed at zero flow. The slope of the line thus obtained corresponded to pulmonary resistance. The values for compliance were obtained similarly by displaying the Pressure-Volume signals and subtracting pressure due to resistance, or by calculation from the subtracted pressure when closing the resistance loop [8].

## RESULTS

The classification that is being used is based on consideration of the vapor pressure of the propellant as well as of the minimal concentration that influences the various parameters relating to the circulatory and respiratory systems. The 9 *low-pressure* propellants are divided into two classes: *Class 1*, those that influence cardiovascular function in concentrations of 2.5 to 5%; and *Class 2*, those that influence cardiovascular and bronchopulmonary function in concentrations of 10 to 20%. The 6 *high-pressure* propellants also are divided into two classes; *Class 3*, those that influence bronchopulmonary function in concentrations of 10 to 20%; and *Class 4*, those that do not influence cardiovascular and bronchopulmonary function in inspired concen-

tration levels of up to 20%. For brevity, the concentrations are identified as follows: 2.5 to 5% to represent a *high* level of toxicity, 10 to 20% as *intermediate*, and the *low* level for those that had no detectable toxicity when inhaled in concentrations of up to 20%.

*Class 1: Low-pressure propellants of high toxicity*

The 5 members are listed in Table I with their respective effects on the various measurements. The characteristic features common to all 5 propellants are tachycardia and hypotension at concentrations of 2.5 to 5%. The effects on respiration are varied; two of them cause depression of respiratory minute volume, three an increase in compliance, and four a decrease in pulmonary resistance. The special features for each propellant are as follows: FC 11 causes the most intense tachycardia and hypotension. FC 21 is the most potent depressant for respiratory minute volume. FC 113 is second to FC 11 in the degree of cardiovascular effect, but FC 113 is more potent than FC 11 in decreasing pulmonary resistance and increasing compliance. Trichloroethane is the propellant that causes a significant fall in resistance and respiratory minute volume but an increase in compliance. Methylene chloride has no effect on respiratory minute volume but has the most potent action on pulmonary resistance and compliance.

*Class 2: Low-pressure propellants of intermediate toxicity*

The 4 members are listed in Table II. The effective inhaled concentrations are 10 to 20%, which influence either respiration or circulation or both. FC 114 affects both and causes specifically tachycardia, hypotension, respiratory depression and an increase in pulmonary resistance. FC 142b causes hypotension but also respiratory stimulation, an effect that is unique, since no other propellants belonging to this class or other classes exert such an action. Isobutane does not influence circulation but increases resistance and depresses respiratory minute volume. FC C-318 causes an increase in resistance but has no effect on minute volume, heart rate or blood pressure.

*Class 3: High-pressure propellants of intermediate toxicity*

The characteristic feature of the 4 members is an increase in pulmonary resistance or bronchoconstriction (Table III). The additional effects vary among the propellants, as follows: FC 12 decreases compliance, reduces blood pressure and accelerates the heart rate. FC 22 does not decrease compliance but influences the other four parameters. Propane has the most limited influence — only bronchoconstriction and respiratory depression. Vinyl chloride affects all three respiratory parameters but not circulation.

*Class 4: High-pressure propellants of low toxicity*

The 2 members listed in Table IV do not influence respiration or circulation, even when inhaled in levels up to 20% concentration.

## DISCUSSION

The most important conclusion drawn from the above experiments is the

TABLE I

LOW-PRESSURE PROPELLANTS OF HIGH TOXICITY (MEAN ± SEM)

| Propellant | % Conc. v/v | Monkey No. | Pulm. resistance | | | Pulm. compliance | | | Resp. min. vol. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control cm $H_2O$/l/sec | Response | %Δ | Control ml/cm $H_2O$ | Response | %Δ | Control ml/min | Response | %Δ |
| FC 11 (Trichloro-fluoromethane) | 2.5 | 3 | 28.6 ± 1.0 | 27.9 ± 0.7 | − 2.00 ± 2.00 | 7.6 ± 0.7 | 7.3 ± 0.6 | + 3.00 ± 3.00 | 699 ± 197 | 744 ± 238 | + 4.00 ± 4.00 |
| | 5.0 | 4 | 35.3 ± 2.3 | 33.0 ± 3.1 | − 7.00 ± 4.00 | 7.0 ± 0.1 | 7.4 ± 0.4 | + 7.00 ± 4.00 | 612 ± 142 | 541 ± 104 | − 9.00 ± 1.00 |
| FC 21 (Dichloro-fluoromethane) | 2.5 | 3 | 27.9 ± 2.2 | 27.2 ± 1.4 | − 2.00 ± 2.00 | 7.7 ± 0.6 | 7.8 ± 0.6 | + 1.00 ± 1.00 | 442 ± 59 | 274 ± 68 | −39.00 ± 10.00 |
| | 5.0 | 4 | 32.7 ± 1.00 | 29.4 ± 1.0 | −10.00[a] ± 1.00 | 7.1 ± 0.6 | 8.0 ± 0.7 | + 8.00 ± 1.00 | 455 ± 91 | 204 ± 24 | −50.00[a] ± 9.00 |
| FC 113 (Trichlorotri-fluoroethane) | 2.5 | 3 | 21.78 ± 3.49 | 19.69 ± 2.71 | − 8.87 ± 4.75 | 6.87 ± 0.43 | 7.27 ± 0.41 | + 5.97 ± 2.30 | 1200 ± 47.3 | 1250 ± 28.9 | + 1.80 ± 1.80 |
| | 5.0 | 3 | 21.58 ± 3.00 | 18.84 ± 2.47 | −12.07 ± 6.64 | 6.67 ± 0.58 | 7.50 ± 0.25 | +13.95 ± 8.80 | 1292 ± 99 | 1302 ± 72 | + 1.10 ± 3.20 |
| Trichloro-ethane | 2.5 | 3 | 20.38 ± 2.56 | 18.52 ± 2.11 | − 8.87 ± 1.07 | 7.20 ± 0.72 | 7.80 ± 0.72 | + 8.49 ± 1.55 | 1352 ± 30.3 | 1213 ± 32.4 | 8.1[a] ± 0.5 |
| | 5.0 | 3 | 21.22 ± 2.99 | 18.08 ± 3.04 | −15.43 ± 2.30 | 7.06 ± 0.56 | 8.16 ± 0.71 | +15.52 ± 3.55 | 1352 ± 30.3 | 1183 ± 11.9 | −12.4[a] ± 2.1 |
| Methylene chloride | 2.5 | 3 | 20.38 ± 2.56 | 18.53 ± 3.43 | −10.43 ± 7.80 | 6.90 ± 0.38 | 7.63 ± 0.47 | +10.90 ± 6.18 | 1280 ± 111 | 1247 ± 79 | − 2.22 ± 2.20 |
| | 5.0 | 3 | 22.83 ± 3.72 | 13.72 ± 3.83 | −32.08 ± 12.93 | 6.90 ± 0.56 | 8.26 ± 0.39 | +20.58[a] ± 5.99 | 1300 ± 100 | 1227 ± 37 | − 5.00 ± 4.20 |

[a] $p < 0.05$.

TABLE I (continued)

| Propellant | % Conc. v/v | Monkey No. | Heart rate | | | Aortic blood pressure | | |
|---|---|---|---|---|---|---|---|---|
| | | | Control beats/min | Response | % Δ | Control mm Hg | Response | % Δ |
| FC 11 (Trichloro-fluoromethane) | 2.5 | 3 | 183 ± 7 | 213 ± 19 | +16.00 ± 7.00 | 91.7 ± 8.3 | 71.7 ± 6.0 | −22.00[a] ± 2.00 |
| | 5.0 | 4 | 175 ± 7 | 239 ± 23 | +36.00[a] ±10.00 | 85.0 ± 5.8 | 45.0 ± 2.9 | −46.00[a] ± 5.00 |
| FC 21 (Dichloro-fluoromethane) | 2.5 | 3 | 145 ± 22 | 168 ± 32 | +15.00 ±10.00 | 87.7 ± 1.1 | 76.2 ± 5.9 | −13.00 ± 7.00 |
| | 5.0 | 4 | 150 ± 12 | 177 ± 17 | +17.00 ± 5.00 | 81.2 ± 6.6 | 60.0 ± 2.0 | −25.00[a] ± 5.00 |
| FC 113 (Trichlorotri-fluoroethane) | 2.5 | 3 | 169 ± 13.65 | 199 ± 19.09 | +18.07 ± 8.14 | 101.67 ± 1.67 | 93.00 ± 3.05 | − 8.54[a] ± 2.36 |
| | 5.0 | 3 | 173.33 ± 12.02 | 221.67 ± 21.67 | +27.85[a] ± 8.58 | 110.67 ± 5.78 | 82.33 ± 2.33 | −25.15[a] ± 4.75 |
| Trichloro-ethane | 2.5 | 3 | 175.66 ± 13.96 | 182.66 ± 13.53 | + 4.23 ± 4.26 | 105.66 ± 0.66 | 95.66 ± 0.66 | 9.44[a] ± 1.01 |
| | 5.0 | 3 | 175.66 ± 10.90 | 202.66 ± 8.97 | +18.13[a] ± 7.75 | 108.33 ± 1.66 | 85.00 ± 2.88 | −21.43[a] ± 3.81 |
| Methylene chloride | 2.5 | 3 | 174.33 ± 15.56 | 187.33 ± 18.70 | + 7.00 ± 4.29 | 100.0 ± 4.58 | 90.00 ± 2.89 | −12.46[a] ± 2.63 |
| | 5.0 | 3 | 174.66 ± 12.66 | 205.66 ± 6.69 | +18.68[a] ± 6.88 | 106.66 ± 4.11 | 86.33 ± 3.48 | −19.05[a] ± 0.95 |

TABLE II

LOW-PRESSURE PROPELLANTS OF INTERMEDIATE TOXICITY (MEAN ± SEM)

| Propellant | % Conc. v/v | Monkey No. | Pulm. resistance | | | Pulm. compliance | | | Resp. min. vol. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control cm $H_2O$/l/sec | Response | Δ | Control ml cm $H_2O$ | Response | Δ | Control ml/min | Response | Δ |
| FC 111 (Dichlorotetrafluoroethane) | 5.0 | 3 | 21.70 ± 1.74 | 22.03 ± 1.71 | + 1.59 ± 1.59 | 6.83 ±0.60 | 6.77 ±0.43 | 0.56 ±2.42 | 1113 ± 52 | 1394 ± 146 | 1.81 ± 6.80 |
| | 10.0 | 3 | 19.75 ± 0.80 | 20.89 ± 1.31 | + 5.58 ± 3.32 | 6.90 ±0.56 | 6.80 ±0.37 | -1.18 ±2.77 | 1507 ± 52 | 1379 ± 123 | - 8.17 ± 9.20 |
| | 20.0 | 3 | 22.42 ± 2.89 | 25.07 ± 3.76 | +11.38 ± 6.01 | 6.63 ±1.17 | 5.97 ±0.61 | 7.78 ±6.80 | 1180 ± 30.1 | 1217 77.9 | 17.60[a] ± 6.10 |
| FC 142b (Monochlorodifluoroethane) | 5.0 | 3 | 28.7 ± 2.5 | 28.7 ± 2.5 | 0.0 ± 0.0 | 8.30 ±0.1 | 8.30 0.1 | 0.0 0.0 | 513 9 | 599 26 | +10.0[a] 5.0 |
| | 10.6 | 4 | 26.7 ± 0.7 | 26.7 ± 0.7 | 0.0 ± 0.0 | 7.1 ±0.6 | 7.1 ±0.6 | 0.0 ±0.0 | 187 ± 82 | 532 ± 101 | ± 9.0 ± 6.0 |
| Isobutane | 5.0 | 3 | 21.36 ± 1.81 | 22.77 ± 1.75 | + 6.75 ± 2.38 | 6.50 ±0.49 | 6.33 ±0.60 | 2.76 ±2.76 | 1110.26 ± 120.03 | 1363.67 159.86 | 5.76 ± 3.12 |
| | 10.0 | 3 | 21.11 ± 1.59 | 25.05 ± 3.68 | +19.39 ±10.79 | 6.83 ±0.41 | 6.37 ±0.63 | 6.70 ±7.38 | 1370 104 | 1233.07 ± 194 | 13.36 ± 5.01 |
| FC C-318 (Octafluorocyclobutane) | 5.0 | 3 | 29.4 ± 1.4 | 29.4 ± 1.4 | 0.0 ± 0.0 | 8.8 ±1.0 | 8.5 ±0.8 | 3.00 ±4.00 | 103 ± 11 | 407 ± 43 | ± 1.00 1.00 |
| | 10.0 | 4 | 28.2 ± 0.4 | 32.3 ± 0.8 | +15.0 ± 2.0 | 5.4 ±1.3 | 7.9 ±0.8 | 4.00 ±1.00 | 113 ± 15 | 421 ± 38 | 5.00 ± 2.00 |

[a] $p < 0.05$.

TABLE II (continued)

| Propellant | % Conc. v/v | Monkey No. | Heart rate | | | Aortic blood pressure | | |
|---|---|---|---|---|---|---|---|---|
| | | | Control beats/min | Response | % Δ | Control mm Hg | Response | % Δ |
| FC 114 (Dichlorotetrafluoroethane) | 5.0 | 3 | 168.00 ± 13.58 | 180.67 ± 6.36 | + 8.64 ± 7.76 | 118.33 ± 3.33 | 114.33 ± 1.20 | −3.27 ±2.10 |
| | 10.0 | 3 | 170.00 ± 14.42 | 188.58 ± 7.26 | +11.90 ± 7.65 | 116.33 ± 5.36 | 105.00 ± 5.77 | −9.78 ± 2.14 |
| | 20.0 | 3 | 173.33 ± 12.35 | 212.00 ± 2.00 | +23.32[a] ± 7.13 | 111.33 ± 3.67 | 87.63 ± 3.71 | −21.22[a] ± 2.56 |
| FC 142b (Monochlorodifluoroethane) | 5.0 | 3 | 186 ± 9 | 188 ± 9 | + 1.0 ± 1.0 | 91.7 ± 9.3 | 89.3 ± 8.1 | − 2.00 ± 1.00 |
| | 10.0 | 4 | 180 ± 9 | 183 ± 9 | + 2.0 ± 1.0 | 93.8 ± 6.9 | 90.0 ± 7.4 | − 6.00 ± 3.00 |
| Isobutane | 5.0 | 3 | 172 ± 5.29 | 177.33 ± 6.43 | + 3.06 ± 0.62 | 115.66 ± 4.70 | 113 ± 2.08 | − 2.13 ± 2.13 |
| | 10.0 | 3 | 182.66 ± 9.96 | 194.00 ± 8.72 | + 6.35 ± 1.89 | 117.33 ± 5.04 | 94 ± 3.79 | −21.66 ± 1.08 |
| FC C-318 (Octafluorocyclobutane) | 5.0 | 3 | 148 ± 20 | 154 ± 25 | + 3.00 ± 3.00 | 80.0 ± 2.9 | 79.0 ± 3.2 | − 1.00 ± 3.00 |
| | 10.0 | 4 | 146 ± 12 | 150 ± 14 | + 3.00 ± 2.00 | 89.2 ± 7.6 | 88.0 ± 7.3 | − 1.00 ± 4.00 |



TABLE III

TABLE III

HIGH-PRESSURE PROPELLANTS OF INTERMEDIATE TOXICITY (MEAN ± SEM)

| Propellant | % Conc. | Monkey | Pulm. resistance | | | Pulm. compliance | | | Resp. min. vol. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control cm $H_2O$/LPS | Response | % Δ | Control, ml/cm $H_2O$ | Response | % Δ | Control ml/min | Response | % Δ |
| FC 12 (Dichlorodi-fluoromethane) | 5.0 | 3 | 26.9 ± 1.2 | 28.6 ± 2.6 | + 5.0 ± 5.0 | 9.7 ±0.9 | 9.0 ±0.6 | − 6.0 ± 6.0 | 500 ± 63 | 500 ± 63 | 0.00 ± 0.00 |
| | 10.0 | 4 | 29.1 ± 0.9 | 33.5 ± 1.2 | +15.0[a] ± 2.0 | 9.0 ±0.4 | 8.0 ±0.4 | −11.0 ± 6.0 | 511 ± 65 | 507 ± 69 | − 1.00 ± 2.00 |
| FC 22 (Monochloro-difluoromethane) | 10.0 | 3 | 20.46 ± 0.96 | 21.57 ± 1.28 | + 5.55 ± 5.55 | 6.83 ±0.83 | 6.66 ±0.66 | − 1.96 ± 1.96 | 1609 ± 312 | 1598 ± 328 | − 1.00 ± 1.00 |
| | 20.0 | 3 | 19.73 ± 0.64 | 23.82 ± 0.59 | +15.89[a] ± 4.83 | 7.13 ±0.90 | 6.65 ±0.73 | 6.40 ± 2.86 | 1563 ± 276 | 1377 ± 239 | −11.76 ± 1.50 |
| Propane | 10.0 | 3 | 21.71 ± 1.24 | 22.08 ± 1.02 | + 1.85 ± 1.85 | 6.23 ±0.67 | 6.13 ±0.73 | − 1.84 ± 1.11 | 1386 ± 99 | 1327 ± 116 | − 8.02 ± 2.32 |
| | 20.0 | 3 | 20.54 ± 1.61 | 22.57 ± 1.29 | +10.33 ± 2.82 | 6.50 ±0.50 | 6.06 ±0.76 | − 7.22 ± 5.64 | 1394 ± 132 | 1127 ± 168 | − 20.10 ± 1.80 |
| Vinyl chloride | 2.5 | 3 | 21.41 ± 0.44 | 21.81 ± 0.41 | + 1.76 ± 1.76 | 6.30 ±0.85 | 6.27 ±0.88 | − 0.66 ± 0.66 | 1417 ± 44 | 1407 ± 72 | − 0.80 ± 2.10 |
| | 5.0 | 3 | 20.70 ± 0.35 | 21.98 ± 0.23 | + 6.20 ± 0.73 | 6.33 ±0.88 | 4.53 ±0.84 | − 2.91 ± 3.56 | 1355 ± 108 | 1274 ± 89 | − 5.80 ± 1.00 |
| | 10.0 | 3 | 20.00 | 23.07 ± 0.97 | +15.35[a] ± 4.83 | 6.33 ±0.88 | 5.90 ±1.23 | − 8.61 ± 6.49 | 1380 ± 12 | 1211 ± 16 | −12.30[a] ± 1.20 |

[a] $p < 0.05$.

TABLE III (continued)

| Propellant | % Conc. v/v | Monkey No. | Heart rate | | | Aortic blood pressure | | |
|---|---|---|---|---|---|---|---|---|
| | | | Control beats/min | Response | %Δ | Control mm Hg | Response | %Δ |
| FC 12 (Dichlorodi-fluoromethane) | 5.0 | 3 | 133 ± 13 | 119 ± 8 | +13.00 ± 7.00 | 81.7 ± 0.9 | 74.3 ± 0.7 | − 9.00[a] ± 2.00 |
| | 10.0 | 4 | 147 ± 9 | 170 ± 7 | +10.00[a] ± 4.00 | 84.9 ± 5.2 | 72.2 ± 6.1 | 15.00 ± 3.00 |
| FC 22 (Monochloro-difluoromethane) | 10.0 | 3 | 167.66 ± 10.40 | 174 ± 10.69 | + 3.78 ± 0.51 | 110 ± 5 | 110 ± 5 | 0.00 |
| | 20.0 | 3 | 167.33 ± 15.07 | 186.00 ± 18.50 | +11.09 ± 4.75 | 112.33 ± 1.45 | 91.66 ± 11.66 | −18.61 ± 9.31 |
| Propane | 10.0 | 3 | 170.33 ± 3.18 | 171.33 ± 3.18 | + 0.60 ± 1.22 | 117.66 ± 3.93 | 116 ± 1 | − 1.41 ± 0.73 |
| | 20.0 | 3 | 173.33 ± 3.33 | 180 ± 0 | + 3.92 ± 1.96 | 117.66 ± 3.38 | 110.66 ± 2.33 | − 5.82 ± 2.87 |
| Vinyl chloride | 2.5 | 3 | 171.33 ± 5.93 | 171.33 ± 5.93 | 0.00 | 113.33 ± 3.28 | 114.33 ± 2.33 | + 0.93 ± 0.93 |
| | 5.0 | 3 | 171.33 ± 5.93 | 173.00 ± 7.23 | + 0.92 ± 0.92 | 110.66 ± 5.21 | 111.66 ± 3.28 | + 0.43 ± 1.31 |
| | 10.0 | 3 | 174 ± 7.02 | 178 ± 6.11 | + 2.14 ± 2.93 | 116.33 ± 5.21 | 106.66 ± 2.73 | − 7.73 ± 6.55 |

TABLE IV

HIGH-PRESSURE PROPELLANTS OF LOW TOXICITY (MEAN ± SEM)

| Propellant | % Conc. v/v | Monkey No. | Pulm. resistance | | | Pulm. compliance | | | Resp. min. vol. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Control cm $H_2O$/LPS | Response | %Δ | Control ml/cm $H_2O$ | Response | %Δ | Control ml/min | Response | %Δ |
| FC 115 (Chloropentafluoroethane) | 10.0 | 3 | 23.36 ± 2.16 | 23.36 ± 2.16 | 0.00 0.00 | 6.07 0.07 | 6.07 ±0.07 | 0.00 0.00 | 1173 ± 93 | 1173 ± 93 | 0.00 0.00 |
| | 20.0 | 3 | 22.90 ± 2.03 | 23.90 ± 1.19 | +2.02 ±2.02 | 6.07 ±0.07 | 6.10 ±0.21 | +0.59 ±3.87 | 1390 ± 123 | 1322 ± 156 | −5.40 ±2.70 |
| FC 152a (Difluoroethane) | 10.0 | 3 | 26.90 ± 1.60 | 26.90 ± 1.60 | 0.00 0.00 | 7.80 ±1.10 | 7.80 ±1.10 | 0.00 0.00 | 783 ± 140 | 767 ± 142 | −2.00 ±1.00 |
| | 20.0 | 4 | 29.30 ± 1.90 | 29.70 ± 1.80 | +2.00 ±2.00 | 7.10 ±0.60 | 7.10 ±0.60 | 0.00 0.00 | 633 ± 96 | 587 ± 117 | −9.00 ±6.00 |

TABLE IV (continued)

| Propellant | % Conc. v/v | Monkey No. | Heart rate | | | Aortic blood pressure | | |
|---|---|---|---|---|---|---|---|---|
| | | | Control beats/min | Response | %Δ | Control mm Hg | Response | %Δ |
| FC 115 (Chloropentafluoroethane) | 10.0 | 3 | 183.33 ± 11.79 | 182 ± 10.58 | +1.49 ±0.94 | 120.66 ± 4.33 | 121.66 ± 5.24 | +0.80 ±1.67 |
| | 20.0 | 3 | 185.33 ± 13.13 | 186.00 ± 12.49 | +0.42 ±0.42 | 120.66 ± 3.38 | 119.33 ± 3.84 | −1.05 ±2.73 |
| FC 152a (Difluoroethane) | 10.0 | 3 | 183 ± 3 | 183 ± 3 | 0.00 0.00 | 97.30 ± 7.90 | 97.30 ± 7.90 | 0.00 0.00 |
| | 20.0 | 4 | 182 ± 5 | 182 ± 5 | 0.00 0.00 | 98.00 ± 7.70 | 98.00 ± 7.70 | 0.00 0.00 |

difference in pattern of action between the two groups of propellants. The low-pressure propellants influence predominantly circulation and the high pressure ones affect respiration. The extent of action is not limited to one function, because there are a few propellants from each group that also influence those of the other group. For instance, the most potent low-pressure propellant that causes tachycardia and hypotension, *i.e.*, FC 11, also depresses respiration. On the other hand, the most potent high-pressure propellant, which depresses respiration, increases resistance and decreases compliance, *i.e.*, FC 12, also causes tachycardia and hypotension. About half of the low-pressure propellants also influence respiration, and a third of the high-pressure propellants also affect circulation.

The second conclusion can be derived from an examination of the four tables which list the classes of propellants. For each pressure class, there are two levels of toxicity. The highly toxic class of low-pressure propellants includes FC 11 and trichloroethane, which are suspected of causing deaths [2,5,9] following the use and abuse of aerosols. The low-pressure propellants of intermediate toxicity include 4 possible substitutes in the event that a decision is made to dispense with one or all 5 propellants that are in the highly toxic class.

The high-pressure propellants consist of four propellants of intermediate toxicity. One of them is vinyl chloride, which has been banned for use in aerosols because of the reports of liver cancer among workmen exposed to this chemical [6]. The two high-pressure propellants in the low-toxicity class can be used as substitutes. It should be emphasized that the level of toxicity is based on results in monkeys reported in this publication. The results obtained from earlier experiments are commented upon in the next two papers which conclude this series.

REFERENCES


1 D.M. Aviado and M.A. Belej, Toxicity of aerosol propellants in the respiratory and circulatory systems, I. Cardiac arrhythmia in the mouse, Toxicology, 2 (1974) 31.
2 M. Bass, Sudden sniffing death, J. Am. Med. Assoc., 212 (1970) 2075.
3 M.A. Belej, D.G. Smith and D.M. Aviado, Toxicity of aerosol propellants in the respiratory and circulatory systems, IV. Cardiotoxicity in the monkey, Toxicology, 2 (1974) 381.
4 R.S. Brody, T. Watanabe and D.M. Aviado, Toxicity of aerosol propellants in the respiratory and circulatory systems, III. Influence of bronchopulmonary lesion on cardiopulmonary toxicity in the mouse, Toxicology, 2 (1974) 173.
5 Federal Register: Trichloroethane (1, 1, 1-Trichloroethane, Methylchloroform) Aerosol Drug Products for Human Use, August 14, 1973, 38 (156) 21935-21936.
6 Federal Register: Vinyl Chloride Containing Self-Pressurized Products, May 9, 1974, 36 (91) 16511-16512.
7 S.A. Friedman, M. Cammarato and D.M. Aviado, Toxicity of aerosol propellants in the respiratory and circulatory systems, II. Respiratory and bronchopulmonary effect in the rat, Toxicology, 1 (1973) 345.
8 A.M. Klide and D.M. Aviado, Mechanism for the reduction in pulmonary resistance induced by halothane, J. Pharmacol. Exptl. Therap., 158 (1967) 28.
9 G.J. Taylor and W.S. Harris, Cardiac toxicity of aerosol propellants, J. Am. Med. Assoc., 214 (1970) 81.