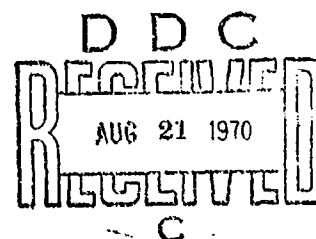


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CENTRAL NERVOUS SYSTEM EFFECTS OF BROMOTRIFLUOROMETHANE

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INTRODUCTION

The purpose of this study was to investigate the central nervous system effects of bromotrifluoromethane (CBrF_3) using electrophysiological methods and to compare these results with exposure to halothane, a close chemical congener and general anesthetic agent. Carter (1969) demonstrated performance decrements in monkeys trained on continuous and discrete avoidance performance tasks when exposed to 20-25% CBrF_3 in oxygen. Van Stee and Back (1969) demonstrated that dogs exhibited excitement and tremors at concentrations as low as 20% CBrF_3 in oxygen and convulsions at concentrations of 50% CBrF_3 and higher. These convulsions were blocked by thiopental anesthesia. Hine et al (1968) further reported that at concentrations of 10% CBrF_3 in air, human volunteers showed decrements in performance.

Those subjects who had previously been exposed to general anesthetics or had consumed moderate quantities of alcoholic beverages were familiar with the sensations produced. These subjects were described as being in the beginning stages of inebriation. It was postulated by the authors that loss of consciousness would occur at 20 to 25% CBrF_3 .

This study was designed to evaluate the electrophysiological changes induced by CBrF_3 in an attempt to better understand the performance and subjective changes reported.

This report contains two sections. The first deals with the electroencephalographic changes induced by CBrF_3 . The second deals with changes induced in the evoked cortical responses.

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ELECTROENCEPHALOGRAPHY

Methods

Six adult beagle dogs weighing 6 to 10 kg and six adult monkeys (*Macaca mulatta*) weighing 2.5 to 5 kg were used. Under thiamylal anesthesia (20 mg/kg), the animals were tracheotomized and ventilated mechanically.¹ A polyethylene catheter was placed in the femoral artery and blood pH was monitored and maintained within normal limits by adjustment of the mechanical ventilator.

Bipolar electroencephalograms were recorded on a six-channel direct writing oscillograph² from stainless steel hypodermic needles inserted in the scalp over the frontal, temporal, and occipital cortex (Caveness, 1962). The animals were immobilized by the intermittent intravenous infusion of tubocurarine. Following recovery from anesthesia a control record was obtained and the animals were exposed to 70-80% CBrF₃ in oxygen and 1% halothane in air for periods not exceeding one hour. Chemically pure bromotrifluoromethane³ and oxygen were metered from pressurized cylinders through calibrated flowmeters into a polyethylene mixing bag and then administered to the animal through the respiratory pump. Halothane⁴ was vaporized quantitatively⁵ in air and administered through the pump. To test for EEG activation, the bell in a spring-wound alarm clock was used as an auditory stimulus and a 100 watt incandescent lamp was used as a photic stimulus.

Results

The EEGs obtained during the exposure were of greater amplitude and synchronization and were dominated by 6-9 cycle per second waves. CBrF₃ did not effect EEG activation in response to photic and auditory stimulation. The results were qualitatively similar in dogs and monkeys although the voltage recorded from the dog's scalp was smaller due to the thicker skull and more prominent overlying musculature.

The results are best illustrated with the following figures. Figure 1 illustrates the induction of the CBrF₃ effect in a monkey. Increased amplitude and synchronization appeared during the second minute of the exposure and became maximal during the third minute. The preexposure EEG amplitude in the monkeys averaged 25-50 μ V and increased to a maximum of 150-175 μ V during the CBrF₃ exposure.

1. Respiration Pump, Model 607, Harvard Apparatus Co., Inc., Dover, Massachusetts.
2. Polygraph, Model 5D, Grass Instrument Co., Quincy, Massachusetts.
3. Freon 1301, E.I. duPont de Nemours and Co., New York, New York.
4. Halothane, U.S.P., Ayerst Laboratories, Inc., New York, New York.
5. Fluotec, Cyprane Ltd., England, dist. by Fraser Sweatman, Inc., Buffalo, New York.

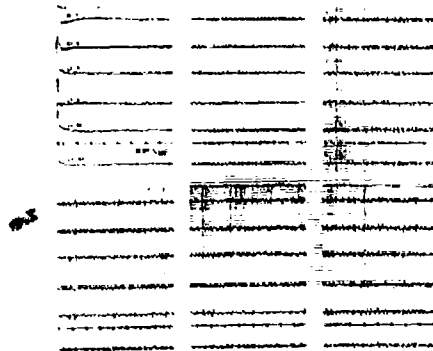


Figure 1. MONKEY E87. THIS FIGURE REPRESENTS THE INDUCTION OF THE CBrF₃ EFFECT. Beginning at the upper left are 0 minute (air), 1, 2, 3, 4, and 6 minute exposure to 70% CBrF₃. Abbreviations used in the figures are frontal, F; temporal, T; occipital, O; right, R; and left, L. Positive is a downward deflection in all figures.

Figure 2 illustrates EEG activation by auditory stimulation. This animal was exposed to 70% CBrF₃ for 21 minutes and then stimulated. The presence of EEG activation, desynchronization, i. e., replacement of the slower, higher voltage waves by fast low voltage activity; is correlated with behavior arousal. Following EEG activation, the animal should be reactive to the environment.

Figure 3 illustrates EEG activation by photic stimulation. The animal was exposed to 60% CBrF₃ for 19 minutes and then stimulated. There was desynchronization of the EEG in response to turning the light both on and off.

Figure 4 contrasts the EEG effects of 70% CBrF₃, 100% O₂, and 1% halothane in the same monkey. Each exposure was for 60 minutes. Halothane produced a delta wave pattern characteristic of sleep or anesthesia (Martin et al 1959). During halothane exposure, auditory, photic or nociceptive stimuli failed to produce EEG activation.

The EEG pattern produced by CBrF₃ could be the result of cortical and/or thalamic depression since the reticular activating system is not significantly depressed.

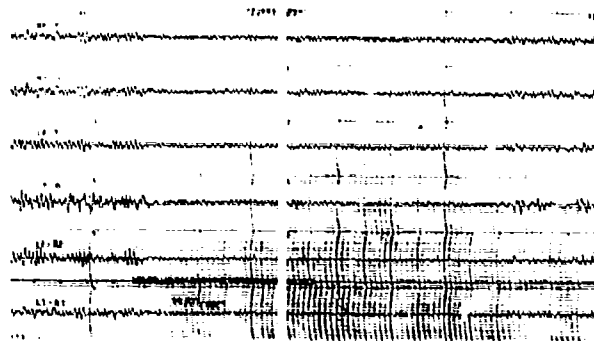


Figure 2. MONKEY E91 WAS EXPOSED TO 70% CBrF_3 IN OXYGEN FOR 21 MINUTES AND PRESENTED WITH AN AUDITORY STIMULUS. The heavy line indicates "stimulus on". Recordings are continuous except for a 5 second interval deleted to compress the illustration.

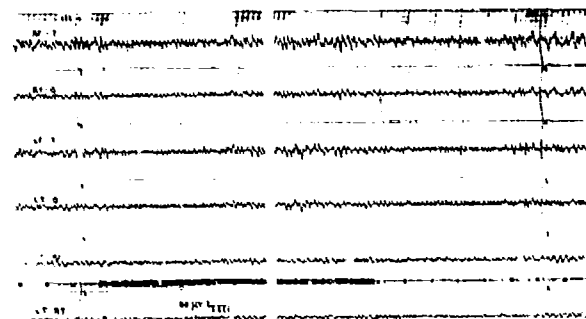


Figure 3. MONKEY E83 WAS EXPOSED TO 80% CBrF_3 IN OXYGEN FOR 19 MINUTES AND THEN CHALLENGED WITH A PHOTIC STIMULUS. The heavy line indicates "light on". A 9 second interval is deleted to compress the record.

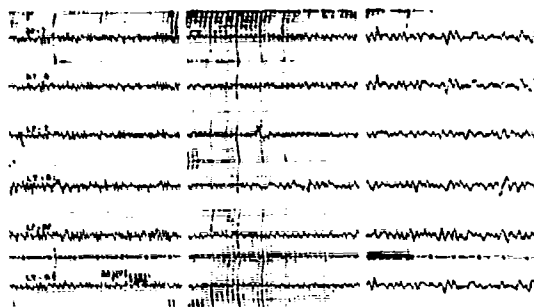


Figure 4. MONKEY E95. THIS ANIMAL WAS EXPOSED TO 70% CBrF₄ AND 1% HALOTHANE FOR 60 MINUTES. These recordings were made after a 20 minute exposure. CBrF₄ is on the left; 1% halothane on the right. A comparable air-breathing control is illustrated in the center.

EVOKED CORTICAL RESPONSES

Methods

To evaluate cortical depression, evoked cortical responses were studied in nine adult monkeys weighing 2.5 to 3.2 kg. Allobarbital^a (diallylbarbituric acid, 100 mg/ml) was administered intravenously in a dose ranging from 0.45 to 0.9 ml/kg. Atropine (0.2 mg/kg) was given subcutaneously to control bronchial secretions. Tracheotomies were performed on all animals and they were fitted with a unidirectional valve that permitted inspiration from a reservoir bag and expiration into room air. The animals were permitted to breathe spontaneously.

Polyethylene catheters were placed in the femoral artery for measurement of arterial pressure using strain gauge transducers.⁷ Standard Lead II EKG and tachographs were recorded from subcutaneous needle electrodes. The sciatic nerve was exposed and two silver wire electrodes were placed for stimulation. The monkey was immobilized in a stereotaxic instrument.⁸ A portion of the skull and dura were removed over the frontal, parietal and occipital areas. A bipolar EEG was recorded from the cor-

6. Dial with Urethane, CIBA Pharmaceutical Co., Summit, New Jersey.

7. Strain Gauge Transducer, Model P23AA, Statham Laboratories, Inc., Hato Rey, Puerto Rico.

8. Stereotaxis Apparatus, Model "U", Baltimore Instrument Co., Inc., Baltimore, Maryland.

tical surface in the frontal area with 2 silver wire ball-tipped (0.3 mm diameter) electrodes approximately 2-3 mm apart.

A silver wire ball-tipped electrode was placed on the postcentral gyrus for recording the primary cortical response. Two stimulating and one recording silver wire ball-tipped electrodes were placed on the occipital cortex for evaluating the direct cortical response. The stimulating electrodes were 1-2 mm apart, and the recording electrode was 3-4 mm from the stimulating pair. Five successive sweeps of the oscilloscope were photographed with a 90 millisecond delay between onset of sweep and stimulus application.

Both cortical responses were monopolar recordings. The indifferent electrode was a stainless steel screw placed in the frontal sinus. Both cortical responses were photographed from the screen of a cathode ray oscilloscope⁹ equipped with a low level differential amplifier. A constant-current stimulator¹⁰ with a positive square wave was used to evoke the cortical responses. Arterial blood pressure, EKG, tachograph and EEG were recorded on a 4 channel direct writing oscillograph.⁸

Figure 5 illustrates the normal pathway and primary cortical response (under barbiturate anesthesia). The sensory nerves in the sciatic nerve are stimulated by a constant current square wave with a frequency of 0.25 cps, 0.5 milliamperes current, and 1 millisecond in duration. The nerve impulses are carried in the primary conduction pathways to the thalamus. This sensory information is then projected to the cerebral cortex and may involve 3-4 orders of neurons (Ganong, 1965).

From the cortical surface, a positive-negative wave is recorded. The positive wave is thought to be the summation of the depolarizations of sensory terminals in the lower layers of the cortex. The negative wave is thought to represent depolarization of apical dendrites ascending from the depths to the surface of the cortex (Li et al, 1956). Cortical depression is represented by a decrease in one or both component waves, the negative wave being the more sensitive.

Figure 6 illustrates the mechanism of production and appearance of the direct cortical response under barbiturate anesthesia (Li et al, 1962). The cortical surface was stimulated with a positive square wave of 0.05 msec duration, 10 milliamperes strength, with a frequency of 0.25 cycles per second. This stimulation produced depolarization of axons in the molecular layer. This in turn produced dendritic potentials in the pyramidal cells which are recorded from the surface as a negative wave.

The origin of the second negative wave remains obscure. However, cortical depression is manifest by depression of one or both waves, the second wave being more sensitive.

9. Oscilloscope, Type 532, Tektronix, Inc., Portland, Oregon.

10. Constant-Current Stimulator, Model 7150, Nuclear-Chicago Corporation, Des Plaines, Illinois.

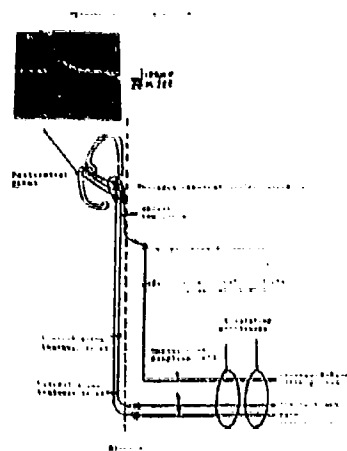


Figure 5. MONKEY J-96 UNDER BARBITURATE ANESTHESIA BREATHING AIR. The photographs of the evoked responses represent 5 successive sweeps of the oscilloscope beam with a 40 millisecond delay between onset of the sweep and application of the stimulus. Positive is a downward deflection in all figures. This drawing illustrates the pathway involved in generating the primary cortical response.

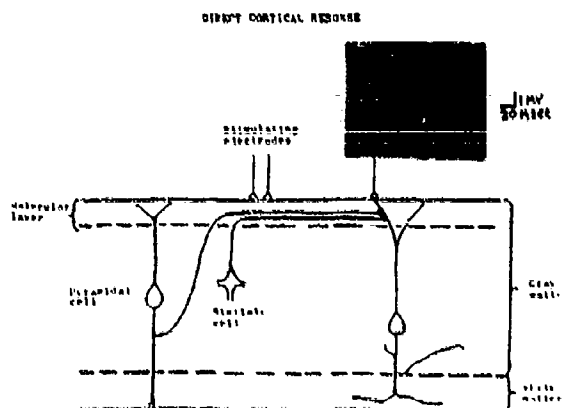


Figure 6. MONKEY K-30 UNDER BARBITURATE ANESTHESIA BREATHING AIR. The photograph represents the typical direct cortical response. The drawing illustrates the pathway involved.

After a 30-minute air breathing control period, CBrF_3 was administered at concentrations of 20 to 80% in oxygen for periods of 10 to 30 minutes. One percent halothane in air was administered for 20 to 30 minute periods. Arterial blood gases were monitored before, during, and after the exposure. However, no attempt was made to correct acidosis or hypoxia if present.

Results

Figure 7 illustrates the EEG and cardiovascular effects of a 30 minute exposure to 60% CBrF_3 in oxygen and 1% halothane in air in the same animal under barbiturate anesthesia. Both agents have significant depressant effects on the cardiovascular system with brachycardia and hypotension. However, the EEG (under barbiturate anesthesia) is unchanged with CBrF_3 , while 1% halothane resulted in total suppression. The suppression of spontaneous EEG activity is a property of anesthetic agents in large doses (Martin et al, 1959). There was no hypoxia, acidosis or hypercarbia present during either exposure.

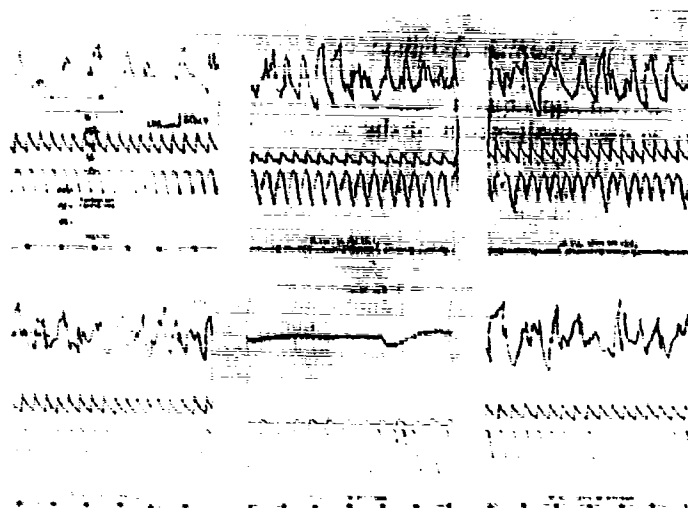


Figure 7. MONKEY H-29 UNDER BARBITURATE ANESTHESIA. The top three segments from left to right represent air breathing control, 30 minutes exposure to 60% CBrF_3 in oxygen, and 60 minutes after the exposure ended. The bottom three segments from left to right represent the air breathing control 60 minutes after the CBrF_3 exposure was concluded, 30 minutes exposure to 1% halothane in air, and 60 minutes after the exposure ended. The irregularities in the tachograph are artifactual. The electrocorticogram is a bipolar recording from the cortical surface of the frontal lobe.

Figure 8 illustrates depression of both the direct and primary cortical responses by 1% halothane in air. At 30 minutes, the responses are approaching the stimulus artifact baseline. These findings are consistent with cortical depression.

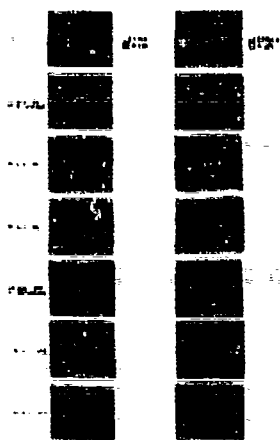


Figure 8. MONKEY H-29 UNDER BARBITURATE ANESTHESIA. This series of photographs illustrates the effect of a 30 minute exposure to 1% halothane in air on the evoked responses followed by a 30 minute recovery period.

Figure 9 illustrates the depression of both the direct and primary cortical responses by a 10 minute exposure to 60% CBrF₃. The effects of CBrF₃ are less striking than those observed with halothane. There is flattening of the second wave of the direct cortical response and a decrease in all components of the primary cortical responses.

Similar results were seen in all animals. When the initial depth of anesthesia was sufficient to cause significant respiratory depression, (respiratory acidosis) and hypotension, 60 to 80% CBrF₃ produced profound hypotension and hypoxia, and the cortical responses and EEG resembled halothane. This probably represented the effects of hypoxia and hypotension rather than CBrF₃.

When hypoxia and extreme hypotension were not produced, 20, 40, and 60% CBrF₃ produced increasing levels of depression of the primary and direct cortical responses. The maximum effect can be seen in figure 9.

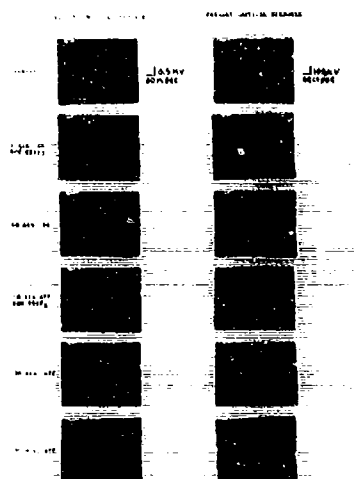


Figure 9. MONKEY H-41 UNDER BARBITURATE ANESTHESIA. This sequence of photographs illustrates the effect of a 10 minute exposure to 60% CBrF₃ in oxygen on the evoked responses followed by a 30 minute recovery period.

A 10 minute exposure was sufficient to produce the effect, but 20-30 minute exposures resulted in greater decreases in the evoked responses.

CONCLUSIONS

The data presented support the hypothesis that CBrF₃ produces cortical depression with relative sparing of the reticular activating system, permitting alterations in performance without loss of consciousness. It is possible that a component of thalamic depression is also present contributing to EEG slowing and decreased amplitude of the primary cortical response. Further experiments are necessary to evaluate this hypothesis.

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DISCUSSION

DR. COULSTON: What would happen, just for instance, if you did these similar experiments with indwelling catheters, etc., on intact, unanesthetized animals? Do you think you'd get the same data?

CAPTAIN CHIKOS (Aerospace Medical Research Laboratory): Unfortunately, you can't do the direct and primary cortical responses in unanesthetized animals because it requires cortical depression and idling population of cells to generate them, so that what you have to do, if you're going to investigate this sort of thing, would be to have chronic indwelling extracellular or intracellular electrodes and measure the activity from the individual cell. At this point in time it should be done. However, it requires expensive equipment and quite a degree of sophistication by the investigators. We are contemplating this at this point. We may let some other national facility do it.

DR. COULSTON: It should be done.

CAPTAIN CHIKOS: It should be done. I agree, but I don't think we have the capability at this time to do it.

DR. HODGE: Is that the same question as what is the barbiturate effect on the reticular activating system in your experiment? Is that the same as Dr. Coulston's question?

CAPTAIN CHIKOS: I'm not sure. I might say that with barbiturates, the reticular activating system is indeed depressed. However, when it is done in air or oxygen, the reticular activating system seems to be very functional up to 80% CBrF₃--the point being that either halothane or barbiturate anesthesia knock out the reticular activating system and allows one to study the cortical activity, per se, without these interfering influences, and we established this protocol in an attempt to study the cortical activity.

MR. WANDS: I think it's important to recall from last year, Dr. Hine's work, presented by Dr. Hodge, that humans exposed did not show truly aberrant behavior in the range between 10 and 15% CBrF₃ in air. They had sensations of slight inebriation, ultimately impending sense of blackout, but during the entire period of exposure, they were able to perform assigned tasks, could take direction, leadership, et cetera, that was given to them, without any evidence of any aberrant behavior.

CAPTAIN CHIKOS: Right. I stand corrected. That's what the paper stated. I was thinking in terms of Dr. Carter's animals that were getting up and crawling around all over the cage. That was directed more in that line than towards the people.

MR. WANDS: Perhaps humans are more inclined to behave themselves even when drunk.

DR. HODGE: I noticed in the post recovery record of the CBrF_3 heart, that there seemed to be a variation in rhythm.

CAPTAIN CHIKOS: Unfortunately, that was a variation in the sensitivity of the tachograph. The monkey EKG is very small, voltage-wise, and the sensitivity knob on the tachograph sometimes goes out of order and we sometimes get a fluctuation in the tachograph record. However, look at the blood pressure, nice and regular, saying no change in rate.

DR. THOMAS (Aerospace Medical Research Laboratory): I just want to recall from last year's conference report that we have seen spontaneous arrhythmias, A-V blocks, spontaneous fibrillation, with this compound in dogs. Now, the old question, of course, in using a compound like this is what risks you want to take? Do you want to get fried? Are you going to take a chance of passing out for a short time? or, if you have time to grab an oxygen mask, you won't have any troubles. It's the best compound we have for putting out fires in oxygen atmospheres, so we are back to the old point of trade-offs. The recovery is so fast that, really, if you can put out that fire before it really gets started and you can go on oxygen quickly, after that you can dump the atmosphere and repressurize. It's between making or breaking the mission. So, it's not a nice compound but it does the job.

DR. HODGE: I suppose the solubility of this compound in blood is extremely low, is that true?

MR. WANDS: It seems to wash out very rapidly.

DR. BACK: Dr. Kaplan is studying that area.

LT. COLONEL KAPLAN (Aerospace Medical Research Laboratory): It is very insoluble in water and blood and we did some tissue studies of brain and heart CBrF_3 content after exposure. During the first minute postexposure, approximately 95% of the CBrF_3 was eliminated from the blood, brain, and heart tissue--a very marked falloff of CBrF_3 .

DR. BACK: That's another paper next year.

MR. WANDS: Ninety-five percent of how much? What's the actual value?

LT. COLONEL KAPLAN: I believe it was in the neighborhood of 300 micrograms per gram of tissue.

MR. WANDS: From what exposure concentrations?

LT. COLONEL KAPLAN: Eighty percent CBrF_3 , anywhere from 5 to 30 minutes.

DR. HODGE: Thank you very much, Captain Chikos. Now, we have a brief period for general discussion on any of the paper or any discussions that anyone wants to bring up at this time. Is there someone who didn't get his question in a little while ago who'd like to raise it now? I would like to ask for one point of explanation. Can someone tell me the difference between the time interval estimation in this carbon monoxide study and the method used by Beard?

DR. MIKULKA: It was essentially identical. The procedure lasted for three minutes and the subject didn't know how long it was working. He was told to go and estimate ten second periods without external or audio cues. In our study he pressed the lever at what he thought were 10 second intervals and that was electronically recorded. After the first estimate outside of three minutes, he was told to stop. He never knew how to gauge estimations. We patterned this almost identically after Beard's work.

DR. HODGE: I'm sorry, I'm not quite with you. What was the stimulus? Where did the time estimation start? Did the man listen to a beep or clock tick?

DR. MIKULKA: No, it was voice command to the subject to start time estimation trial. In each testing interval the subject had five tracking tasks, about a minute per shot on a control stick, and then went to time estimation back to tracking, and it took 15 minutes for the whole block of time. After tracking was finished, he rested a few seconds and then I said, "All right, on my signal, you must start time estimation", and then I'd give them GO. He then started, however he did it, to estimate ten seconds, and then tapped a switch with the right hand and started to estimate ten seconds again. So, after my initial signal, it was self-repeating on his own signal. After he did the first one past the three minutes we said, "Okay, stop". The data was the mean-time averaged for all those intervals. I hope that clarifies it.

DR. HODGE: Thank you.

LT. COLONEL STEINBERG: In dumping this Freon into the cabin atmosphere-- this has nothing to do with the pharmacology or physiology involved, but the mechanics, -- is there any system that's been fixed on yet? Is it a light sensing system? Have you found any one system to be better than any others, or haven't you decided on a system yet?

DR. BACK: There are pros and cons as to how--whether you want to dump it automatically or not, so that some people think that the pilot ought to be the actuating device in an aircraft or in a close environment, and the other way is to do it by UV sensors and that will dump it in a matter of 20 milliseconds. Now, you've got all kinds of problems, depending on use. If you're talking about a 747, which the FAA was interested in equipping with CBrF_3 , you can imagine that if they dump the whole contents to reach a 7% concentration in the entire cabin and it's done from the periphery

of the 747 cabin, obviously, the guy over there on the side would be getting maybe a hundred percent in his face, while the guy out here on the aisle seats wouldn't be getting a fraction of that for some milliseconds. So you would have a total gradation of a hundred percent on the sides to 7% in the middle of the room.

MR. WANDS: Extending over what period of time?

DR. BACK: Well, extending over the period of time that it takes to deliver it and the time it mixes with the cabin air. If you're in a crash situation, how long does it take to break apart? I don't know. Of course, this could have been lifesaving, for instance, in the 727 crash at Utah, because these people weren't all killed by the impact. Most of the people died from fire and smoke after the impact. Some of them were out of their seats, as a matter of fact, and could not get out. The matter of how you do it is depending on what the situation is. Some people think, especially in space cabins or in aircraft, that the pilot ought to activate the system because you're worried about false alarms from the sensors. We had this problem with water. Some of my sergeants will attest to that. They were deluged with 350 gallons of water in 20 seconds. In fact, Colonel Kaplan and Captain Chikos here, they're pioneers in this. They actuated the system in the dome inadvertently in one instance by a UV light source which they thought was a flashlight, but, it was a device for testing the UV sensors built in a flashlight case.

LT. COLONEL KAPLAN: There are some other systems too.

DR. BACK: There are other systems, smoke sensors. This is an area which the people in Ground Safety, Ground Support, are working on at Wright-Patt and other places. I can't give you all the details, but they're looking at all the sensors - smoke, flame, spark, even temperature.

DR. THOMAS: There's only one problem with automatic triggering. In aircraft, the no smoking signs must be on all the time. In aircraft, you know, you don't have the problem of oxygen rich environment and I think there's plenty of time for the pilot to punch a button. In spacecraft it's a decision we'll have to face.

DR. BACK: The pilot is a far distance from where the fire may be in the 747. All I'm saying, the alarm is an easy way out in the engine nacelle or someplace like that, but it sure is a devil of a tough problem when you get back with that cast of hundreds of passengers.

DR. THOMAS: Maybe temperature sensors wouldn't be so bad, really, placed across the cabin to sense hot spots.

DR. HODGE: Mr. Wands says it's maybe a panacea in a crash situation.

CAPTAIN SCHWARTZ: Dr. Back, you're going to be using behavioral systems for testing environments with monkeys in the future, I'm sure. It seems that you're under fire from the psychologists saying that under threat of death in the last breath, they're going to pull this lever. I am not sure that it is because they get this response

or they know the 15 minutes is coming so they start working, shock or no shock. Is there any way to calibrate the system so that you know significant responses and you know that your compounds are doing something to them?

DR. BACK: Well, it's pretty obvious that we're using a very robust situation here, as Major Carter indicated. It's obvious, though, the CO animals are still responding where the CBrF₃ animals were not responding to the same sort of task stimulus, so it is very robust, agreed, but it's the only thing we had at the moment. Now, we recognize full well that we need something very much more sensitive and we are working on that right now--Dr. Carter went down to Arizona State University to test a new system. We think we have a much more meaningful task now, a more sensitive task, in which the animals are given a time out and time in period, and they are still negatively reinforced. In other words, we are still using shocks because I'm always worried toxicologically about loss of appetite in a positive reinforcement situation. After all, if you take an animal's appetite away, he's not going to perform just to get food, so you're always going to get a depression of effort from a compound which does work against appetite. So we still are keeping with the negative reinforcement. But it looks like this test with the time in and time out interval, where the animal is given a start cue, and he's got, say, from the third to the fourth minute with time out. On the fourth minute he starts working, and he must keep working at an increasingly rapid rate until the last 3/10 of a second or he is given a shock if he isn't pressing at that last 3/10 second. This has been tested out with decaborane, as a matter of fact, and it looks like a number of things can be gleaned from this. Number one, the animal may be so confused that he works in the time out area, from the third to the fourth minute. He's pressing levers and he doesn't have to. And then the other thing is the latency with which he starts to work after the fourth minute, and then the rapidity with which he goes towards his final goal which is the last 3/10 of a second. Now, that last 3/10 of a second can be changed as the compound dictates, and I think this is going to be a much more meaningful way of doing it. We're still going to have some discrete avoidance tasks piled in on top of this, but this looks very, very sensitive, and it has a time estimation in it which everybody looks at as being one of the important criterion for toxicological study.

MAJOR CARTER: There are disadvantages to the type of task we're using, and the one Dr. Back is talking about has an advantage. When I am exposing the animal, -- let's say he misses the auditory cue, he gets a shock. He doesn't know exactly why he gets the shock so he just starts beating heck out of the lever. You know, he just presses that lever and he misses the next one, and he presses it that much harder. So, really, over the entire 15 minute period, when you superimpose results one on top of the other as we did here, it confuses the issue. I think if I did it over again, I'd only have maybe auditory and visual, present it once every 30 seconds, and so forth; whereas, the new task Dr. Back talked about, the animal only gets one shock regardless, so you can determine performance over this entire period without the animal getting reinforced right in the middle and confusing the whole issue.

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