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Methodology for the Study of Toxicology in Combustion: Application to PVC

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I will try to give some idea of how we study toxicology, what it means, and I will then discuss some aspects of our recent studies with poly(vinyl chloride) polymers. I should like also to discuss briefly the analytical methods used. May I point out that during the last three and a half years, we have investigated about 500 fire injuries and deaths. This work is done in collaboration with the city and county fire services by using two-way radio. Two months ago, we began what is probably the most important aspect of this work: paramedical teams arriving at the scene of the fires now take blood and breath samples from the fire victims the moment that they are removed from the fire scene, thus enabling us to get some idea of the immediate effects. Previously, we have been obtaining this sort of information after the

individuals have reached the hospital, by which time they have been put on oxygen and hyperventilated so that it does not reflect what happens during the fire.

In the area in which we are interested, we are concerned with the materials in a built environment. We use the fire injury and autopsy data to give us some information about human behavior. I might point out that it is my firm belief that if we had to make a choice today, I would preempt, without exception, for a public education program, for early warning detectors, and suppression systems.

In our state, all the hospitals and nursing homes now have this. Smoke detectors are required to be put in all new homes and in all homes when they are sold. All high-rise buildings not only have smoke detectors, but also positive pressures in the fire escape ways, sprinkler systems, and safe areas. A public education program has reduced our fire deaths from 16 to one per year in a city of 350,000 during the past three years, and the fire injuries have been reduced from over 500 to less than 100. I think we can do a great deal by means of education.

There are two periods involving fires: in the first period, the individual can leave a fire area on his own; in the second period, an individual cannot leave on his own; he is incapacitated by some of the gases present.

We are not at all interested in the "upside-down animal approach" being defined as the LD_{60}, which is commonly used in many parts of the world. The LD_{50} does not tell us when or why the animal dies. I am more interested in those factors which prevent safe survival. We define survival as the ability for an individual to recover. Not only is the period of time during fire exposure considered, but also short-term disability and long-term disability. If an individual dies post-fire in a period long before the period in which his normal life span expectancy would be, then he is a fire victim. I will talk more about this later.

I might point out that in nonfire exposures to carbon monoxide in which an individual is exposed to a lethal or a comatose level, so that he is knocked down, he is unconscious. About 80% of such individuals will recover immediately or within a few days following exposure. However 15 to 20% of those people between 9 and 15 months later suddenly develop dementia and the "shakes," dying shortly afterwards. A pathological or neuropathological examination of such people shows a demyalination of the central nervous system in the protective sheaths, and infarcts in the brain. The individuals have died of delayed effect of carbon monoxide. Many people in fires actually die long before they come in contact with flame. In some work described at this meeting, and in some of our own work, it was shown that the

notation that carbon monoxide is the primary killer in fires is false. In fact, if we consider two groups of individuals, those who die within 12 hr, usually at the fire scene, die of smoke poisoning and asphyxiation. This accounts for about 53% of the deaths. Respiratory tract damage is fairly slight. In the second group of individuals, the respiratory tract damage becomes greater later, once they are taken to the hospital and treated.

In 1963, Schulty discussed the level of carbon monoxide necessary to kill animals as being about 70%. Carbon monoxide has a binding capacity with the hemoglobin in the blood to form carboxyhemoglobin which is 280 times that of oxygen; once so bound, it is extremely difficult to unbind.

In an examination of fire victims, 185 cases were autopsied and only 24%–45 cases–had a carbon monoxide hemoglobin saturation greater than 50%. That is below the level which causes death. Indeed, another 34%–64 of the victims–had between 11 and 49% carbon monoxide saturation. In addition, 11% had 7% to 10% saturation–the level of the two-pack a day smoker. Clearly, carbon monoxide itself does not cause a high percentage of fire deaths. In fact, in the case of someone smoking cigarettes, and falling asleep, where there is a long smouldering period and usually a high concentration of combustion products inhaled through the nose and mouth, when the individual suddenly awakens, realizes he is in trouble and takes a few steps before collapsing, we generally find such an individual a few feet away from the source of ignition. If the victim has been drinking alcohol, instead of finding a 45% or 50% level of carbon monoxide, we find that the carbon monoxide in saturation levels will be about 30% or less. There is a strong synergistic response between blood alcohol, if the blood alcohol is greater than 0.1 vol %, and carbon monoxide.

There are many plastics, and we need to try to assess human response to them. A simple test is the following. A rat inhales the smoke and, if he falls off, it says "no", whereas if he does not fall, it says "yes", that would be an extremely simple test method. Unfortunately, it does not work quite like that.

Another way of looking at this schematically is to use the early approach, or the LD_{50}. Here the individuals are exposed to the smoke, they are incapacitated and individuals can be counted. It does not tell us much, however; it does not tell us when or how they die, or the mechanism of their death.

THE MODEL

In the type of work we are doing, also Dr. Jouany and others, exposure of an animal is used to model the human being. Two points

are measured: first, a physiological–or a behavioral–endpoint, and, secondly a bioassay endpoint.

I will try to define how we develop a model. First, exposure conditions have to be defined. For such a definition we look at the type of work being done by Dr. Woolley, by the Bureau of Standards, South-West Research, and in other large-scale fire tests. Secondly, we have developed a simple clinical examination which tells us quickly the physiological status of the test animal; thirdly, a systemic analysis and, fourthly, we assess the relative toxicity of different materials by comparing to knowns–the effect of carbon monoxide, of carbon monoxide plus carbon dioxide, of carbon monoxide-carbon dioxide, temperature on HCN, etc. Having developed those models the status of the animals in the laboratory test can be assessed.

Next, exposure conditions must be defined. We are extremely concerned about the heat flux, radiant energy imposed on the sample, mass of the material, smoke density, and mode of combustion. Materials, of which there are a number of different types, will vary widely with respect to the above factors.

For instance, if we consider wood, in the United States there was an attempt to say that materials must be no more toxic than wood. That was fine for the plastics industry because it turns out that wood is one of the most toxic materials known to man. If wood is exposed at 2.5 W/cm^2 radiant flux, in a nonflaming mode, the animals are incapacitated at a carbon monoxide level of 7%, equivalent to a two-pack-a-day smoker. The animals are incapacitated because they are exposed to the 3-C unsaturated aldehyde acrolein, an extremely strong lachrymator, to acetaldehyde, propylaldehyde, and butyraldehyde. However, if that same piece of wood is exposed to 7.5 W/cm^2 just below the ignition point, the animal will now develop a syndrome showing a 70% carbon monoxide saturation. The aldehydes have been formed, but they have been destroyed in the flame front, or the radiant heat flux area. Thus, there are two different modes of exposure. With a polyurethane there is a critical temperature of about 485°C, below which large amounts of HCN are not formed, but above which they are.

In addition, we have developed a simple examination which people can be trained to carry out in 5-10 sec, so that they can analyze the condition of the animals. This involves no more than looking at the posture of the animal. The rat is held about 1 ft above a table upside down and dropped on to the table. If the animal falls "plonk" and does not turn over, that tells us immediately that there is physiological block to the central nervous system. An average animal will land on all fours. If he does land on all fours, the time taken for him to move out of a 10-in. circle drawn on the table is measured. A normal animal will take 3-5 sec to move out of the circle; if he does not move out of the circle, or

is delayed, this tells us again that something is wrong with his central nervous system, perhaps affecting motor conduction. We can also pinch his tail to see whether the animal responds to pain; or we can see whether he responds to a light flash. If we find that these various, quickly assessed functions are abnormal, we can then ask why?

For systemic analysis we use the behavior point, as measured by the clinical endpoint, an organ system response, and a graded toxicant response. The objectives are to assess the ability for a human or an animal to escape untoward physiological response. If he is shocked, he does not want to be shocked but wants to get out. If the temperature increases, can he get out? We are interested not only in death but the two most important factors of the ability to resuscitate immediately and the long-term morbidity.

It is difficult to model any real fire situation because real fires vary so much. For instance, in a typical home fire starting at night in a two-story home in which the occupants are asleep with the bedroom doors closed, the mean survival time is about 10 min. If the bedroom doors are open, there is only about 4 min in which the occupants can get out. If there is a detector in that house, which measures the products of smoke and of ionization, there will be a warning which gives the people more chance to get out. As I pointed out, I will look for a graded response, a limiting effect, and I will try to measure quantitatively and qualitatively the differences in this response.

What is a graded toxicant? A good example is carbon monoxide. There is a wide range of concentration which causes a set of effects, and at the proper time this set can be reversed. It may vary, but people have an ability to acclimatize and to adapt. As people grow older, they tend to slow down, which means that an older person has less chance to escape if he is exposed to fire. A woman, during the latter period of a menstrual cycle, at a high altitude may have a drop in hematocrit of four or five points; her ability to escape from a fire at that time of her monthly cycle is greatly diminished.

Now we come to the limiting toxicant. A good example is hydrogen cyanide, or the 4-α-bicyclophosphate ester we discussed some months ago. These materials in a very low concentration can incapacitate or kill. There is no acclimatization nor adaptation.

In our response, let us suppose we measure the percentage of carboxyhemaglobin as a function of a given concentration in the environment, considering some physiological response which occurs at a certain level over a certain period of time. If we run an experiment in which we monitor the carbon monoxide in the air, with a certain decrease in time, then we need to start to look for X, defined as the limiting toxicant, a material which either additively, or synergistically affect the individual. A good example of this is hydrogen cyanide,

which affects transfer of oxygen from the blood to the tissues. This is a form of histotoxic anoxia. If hydrogen cyanide is present and the cytochrome oxidase is knocked out, oxygen is present in the blood but it cannot transfer. This means that there is not just a normal effect of the carbon monoxide but an additive affect. A given toxicant, X, may affect a certain percentage loss of pulmonary, cardiovascular, central nervous system efficiency, but it may not affect the neuromuscular system, so that the two toxicants together may be an extremely potent mixture.

The premise for studying toxicology on a relative basis is to take something like carbon monoxide and determine what levels bring a certain effect, then look at the limiting effects if differences are found, identifying and quantifying these limiting toxicants.

An animal model is needed in order to do this. The animal has various probes and electrodes in it, certain systems are amplified - we now have them computerized - and the physiological status of the animal can be monitored. Our model is a rat, and we are monitoring respiratory rate, electrocardiogram, blood pressure, electroencephalogram, the brain waves, the visual evoked response, a visual response, and nerve conduction velocity. The brain may tell the feet to move but the feet have to receive the message; there is a certain rate at which the message is transferred along the nervous system. The measurements include time, respiratory rate, the heart rate—similar to those shown by Dr. Jouany.

In the model, the animal was taught in 10 min to keep his foot off the platform because every time he touches it he gets a shock. There are electrodes to record the electroencephalogram, an impedance nomograph to measure respiratory rate, and leads for cardiogram; also the animal is cannulated from the femoral artery to a polyethylene tube so that we can take blood from the animal during exposure, monitoring the changes in blood chemistry, both blood gas analysis and serum enzymes. The animal can live a normal lifetime with the electrodes in position.

In one of the earlier model systems with the animal in a cage, there was a variable flux heater—2.5 W is only one flux level—and we must use levels putting the animal into the smouldering the flaming and the post-flaming ignition. We monitored oxygen, carbon monoxide, and carbon dioxide continuously, and HCl and HCN on a batch process, pulling out all the other gases through solid support with a peristaltic pump, later carrying out computer analysis on these materials.

A series of the animals was exposed at levels up to 2500 ppm of pure carbon monoxide. At a certain level of carbon monoxide loading, the animals lose the ability to keep their foot off the electrified platform. Similarly, as the carbon monoxide builds up, the oxygen

decreases, so that we have a measure of oxyhemoglobin and carboxyhemoglobin.

At 1000 ppm carbon monoxide, avoidance is not lost after 70 min, nor is there a reduction in nerve conduction velocity. But with the 2500 ppm to 3000 ppm level, avoidance is lost–49.4 ± 2%–and nerve conduction velocity is lost at about 70% loading, also after 70 min. At the point at which the animal loads, within a few percentage points, he goes from a few failures to the stage at which he continually drops his leg and cannot avoid a shock. It is a very sharp, highly reproducible endpoint.

A computer printout of the total effects of this animal response is obtained. For instance, in the response to 1500 ppm carbon monoxide by ten animals as a function of time, carboxyhemoglobin is built up. Initially, the respiration rate is high and then it drops. The heart rate decreases continually and, most important, there is a decrease in the blood pressure.

The type of work we do on every animal, gives us a complete read-out at 2-min intervals, all the results being computerized. We obtain the blood pH, the partial oxygen-carbon dioxide base excess, bicarbonate, oxygen saturation, total carbon dioxide, oxyhemoglobin, hemoglobin, carboxyhemoglobin, red cells, white cells, hematocrit, and mean cell volume. We know exactly the status of the animals, and this is exactly the same as the status of any of us in hospital under intensive care. We know the environment; we know the animal.

APPLICATION TO PVC

In the exposure to a rigid, 95% poly(vinyl chloride) during the first few minutes there is a drop in pH and pO_2, with an increase in pCO_2, a change in bicarbonate; which the animal is quite quickly unable to buffer. He is overwhelmed and he goes from a respiratory to a metabolic acidosis. To give some idea of the total status, of the animal there is the compensation of the pCO_2, the pH, the bicarbonate; the animal can be put into a respiratory acidosis, a metabolic acidosis, or an alkalosis. The computer shows where the animal is as a function of exposure time and environment.

In addition, with carbon monoxide there is a tremendous reduction and loss in nerve conduction velocity. We now know that there is a loss in blood pressure, which is related to the blood flow to the brain. If the blood flow to the brain is depleted for 2 or 3 min the result is either death or permanent injury.

If a normal, alert animal, is dropped on the table from a height of 1 ft, he will be out of that circle, exploring, defecating, and urinating

within about 3-5 sec; he is alert, his ears are up, and his posture is good. An exposed animal will not make it; he may stay in the circle for 3 min, his posture is poor, and something is wrong with him.

If we consider the pathology, the result of an exposure to poly(vinyl chloride) shows that there is edema in the tracheobronchial tree. In some case there is a clogging up of subparticles. If only hydrogen chloride were being put into the animal, there would be development of laryngospasm, the larynx would close, and the HCl would not go down into the lungs. Our studies have shown, however, that not only is there HCl, but benzene and other compounds. These other materials depress the laryngospasm, so that there are particulates–both solids and aerosols, containing HCl in the 0.3-0.5 range getting into the lungs. Autoradiographic studies are now being done to show the locations of these particulates. This is the reason for the rapid drop in pH.

With an animal which has survived the initial exposure, there are some subparticles and a massive hemorrhage which may occur 4-5 days after exposure to a PVC sample containing antimony. In the lungs taken from a normal animal, the air sacs are in a normal area - where the blood is changed, where the oxygen is changed at the alveoli capillary region.

When there is a pulmonary edema caused by exposure to poly(vinyl chloride), there are now areas of fluid present, and where there is fluid, gases cannot be exchanged. Many other injuries are to be found in the tissues following exposure to PVC fires, for instance, hyperplasia, which is a completely abnormal tissue condition. We are now investigating hundreds of animals to see whether this becomes anaplastic or forms cancers after long periods of time, given a single exposure.

Another area about which we have been concerned is the effect of the vapors from poly(vinyl chloride) on the tracheobronchial tree. After exposure to PVC, this columnar epithelium is gone 4 hr after exposure, and there is a protein exudate with complete necrosis of the columnar epithelium cells. In addition, when we re-examine any surviving animals later there is a development of completely abnormal columnar epithelium cells, and a high degree of secretory cells. We are now following this in cats and monkeys to determine the long-range effects.

There have been a number of PVC fires in the United States involving injury to firemen. We now have over 100 medical histories, with 300 or 400 more becoming available to us in the next two months from back issues. In many of the PVC fires two things have happened: first, the firemen involved become disoriented and, secondly, they have an extremely low carboxyhemoglobin–usually less than 20%

saturation. They usually show signs of dizziness with this disorientation.

In a new development of our investigations with animals, a series of experiments with the use of both a rotating wheel and head-only exposures of animals has been begun. With these cages, there is a variety of sets of equipment: a physiogram, which measures and records the various biological functions, which then are put into a computer. There are a series of gas chromatographs which have a peristaltic pump, which also goes to the computer. The computer recording the material has a dual disk system (15 megabit).

Not long ago, in Pittsburgh, some questions were raised about the effects of carbon monoxide, carbon dioxide, and other materials. As a result, we have run some experiments, and the results enable me to say that up to 8 vol % of carbon dioxide there is a change in respiratory rate, but the loading effect of carbon monoxide is absolutely identical with time, and the endpoints are identical. If we use acrolein, the respiratory rate can be reduced by 50% at a level of 18 ppm, but the uptake of carbon monoxide is not affected. With polyquinoxaline at different flux levels, there is development of a syndrome such that, with increasing flux levels, there is carbon monoxide intoxication only. If, however, we consider the effects with poly(vinyl chloride), there are three fluxes, and flaming and nonflaming exposures. Concerning the blood chemistry, the higher the wattage of the radiant flux to which there is exposure, the lower the pH. Up in the 5-7 W range, about 800-1000°C, an increasing amount of HCl is produced early with the development of metabolic acidosis plus benzene. If we consider it as a function of percentage of carboxyhemoglobin and mass lost as an effect of exposure, with increasing exposure, there is a greater carboxyhemoglobin and more material lost. This is what would be predicted.

The analytical system allows the volatiles to be studied. This is done by a computer-controlled gas chromatograph-mass spectrometer (GS-MS) assembly. This picks up carbon monoxide and methane, for which there is poor trapping efficiency with infrared. For the liquid materials we now use a high-pressure liquid chromatography and mass spectroscopy. Recently we have started to interface a chemical ionization mass spectrometer to the high-pressure liquid chromatograph, thus enabling us to begin to look at the aerosols in the way we previously looked at the gases.

Where we have the condensables, we may want to make derivatives of them, to separate the volatiles and the condensables, finally investigating the char. Doing all this, the gases, the volatiles, the residues, has enabled us to study some 15 polymer systems by pyrolysis, oxidative degradation, and flaming combustion. On the basis of

elemental analysis, quantification of each of these components is between 90 and 100% of the mass balance.

The system itself involves the source, the trapping system, the GC–a preparative GC, so that if there are small peaks, repetitive trapping can be done back into the GC–the mass spectrometer, a computer for which we use the Kovats retention indices (the Aldermastin and the McClafferty file) with about 40,000 compounds on computer tape.

Primarily, we search molecular weights. Since there is chemical ionization, there is the (M - 1), (M + 1) or molecular weight. Secondly we search major mass fragments, then retention indices, finally coming out with the same compound. Thus, we have three different modes of identification available.

With the work on poly(vinyl chloride) we have also reached the stage of doing TGA and DTA analysis, kinetic analysis plus the effluent gas, residue, and aerosol.

A molecular leak valve was also put on to the thermal analyzer, with a new inlet system which has a separator jet or capillary columns directly into the ion source. Such a system allows us to follow something like PVC, and get with a heating rate of 10°C/min, the formation of HCl with a little unsaturated material, the benzene and the toluene. The comparison shows how the different products are formed.

CONCLUSIONS

In summary, we developed a laboratory system which allows study of flaming combustion, smouldering combustion, and pyrolysis. We can analyze the products being produced in real-time-exposed animals and determine their status, giving us some appreciation of the animal response.

In addition, the real-life situation of the fire victims can be studied and compared with the results from the animal experiments. With these results, and with the engineering approach, over the next few years we should be able to obtain much more information about how materials decompose.