of excess argon (dissolved in the mineral from the magma before eruption); however, sanidine has been found to be remarkably free from this problem. Furthermore, the abundant sanidine in all the samples permitted the use of this mineral exclusively for the dating process.

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Extreme Toxicity from Combustion Products of a Fire-Retarded Polyurethane Foam

Abstract. *The products from nonflaming combustion of wood and a trimethylolpropane-based rigid-urethane foam that was not fire-retarded produced elevated carboxyhemoglobin levels but no abnormal neurological effects. However, when this type of foam contained a reactive phosphate fire retardant, the combustion products caused grand mal seizures and death in rats. The toxic combustion product responsible for the seizures has been identified as 4-ethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2.]octane-1-oxide.*

The utilization of plastics and polymeric materials in our man-made environment is increasing yearly along with the likelihood that they will become involved in industrial or domestic fires. The fire hazard of a plastic material was demonstrated by the Cleveland Clinic fire in 1929. A highly combustible nitrocellulose material, in the form of x-ray films, caught fire, and 125 persons died. Most of the deaths were due to smoke inhalation rather than flame contact (*1*).

Depending upon anticipated use, some polymeric materials are now required by law to pass various flammability tests (*2*) of ignition, surface flame propagation rate, fire endurance, and heat contribution (*3*). In order to pass these tests, many materials require the addition of a fire retardant. However, the relative toxicity of the combustion products of fire-retarded materials compared to those which are not fire-retarded has not been widely investigated. A meaningful risk analysis that takes into account the reduced ignition probability and flame spread characteristics, as opposed to the possible increase in smoke-induced toxicity, cannot be conducted until such studies are completed. We report that in the case of a laboratory-formulated fire-retarded rigid-polyurethane foam, the physiological and toxicological effects of its combustion products proved fatal in a matter of minutes. The same rigid-polyurethane foam, without fire retardant, produced nondebilitating carboxyhemoglobin (COHb) levels but no other observed signs of toxicity.

Animals were exposed in an Aminco chamber developed at the National Bureau of Standards for smoke density research. The chamber was equipped with a heater modified to give a radiant-energy flux of 5 watt cm^{-2} (*4*). For each smoke exposure, four male pigmented Long-Evans rats were held radially nose-to-nose in slings that permitted free movement of legs and head. Thus, all four animals inhaled smoke from the same breathing zone. One of the animals had an intra-arterial cannula for removal of blood. These samples were analyzed for hemoglobin (Hb) concentration and percentages of COHb and oxyhemoglobin (O_2Hb) with an Instrumentation Laboratories model 182 CO-oximeter by a spectrophotometric technique (*5*). Hemoglobin concentration and percentages of COHb and O_2Hb were determined from samples drawn before and periodically after exposure. The rate of return to a baseline percent COHb level was used to indicate efficiency of pulmonary function.

Eight animals were exposed to smoke from samples of Douglas fir (two trials); 12 were exposed to smoke from polyurethane foam that was not fire-retarded (three trials); and 8 and 12 animals were exposed to smoke from the same foam after fire-retarding with *O,O*-diethyl-*N,N*-bis-(2-hydroxyethyl)-

Table 1. Formulations of rigid-polyurethane foam; FR, fire retardant (percentage by weight); MW, molecular weight.

Substance	Parts by weight		
	0% FR	4% FR	8% FR
Polymethylene polyphenyl isocyanate	100.5	100.5	100.5
Propoxylated trimethylolpropane (MW 340)	75.0	68.7	62.25
Silicone surfactant	0.9	0.9	0.9
Trichlorofluoromethane	21	21	21
Triethylene diamine	2.65	2.65	2.65
O,O-Diethyl-*N,N*-bis(2-hydroxyethyl)-aminomethyl phosphonate	0	8.0	16.25
Phosphorus (% by weight)	0	0.48	0.97

aminomethyl phosphonate (4 and 8 percent, respectively). The formulations for these foams are given in Table 1.

After exposure, all animals except the cannulated one were removed from the slings and placed in a 92 by 122 cm corral, where they were examined and behavior was recorded on movie film. The results of the behavioral assessment of animals exposed to smoke from each of the three materials and of controls exposed to CO are summarized in Table 2.

Inhalation of wood smoke resulted in severe respiratory distress, manifested as rib retraction on inspiration, slowed respiration rate, and marked flaring of the nares and gasping. The essential gross pathological changes were confined to the lungs. There was dense pulmonary edema associated with a light pink coloration suggesting CO intoxication. Oxyhemoglobin levels were low and COHb unloading was abnormally prolonged. In addition, particles of brown pigment were seen at the level of the laryngeal folds and epiglottis.

All responses of animals exposed to smoke from untreated polyurethane foam were those expected from the mild to moderate elevation of COHb levels (28 to 33 percent). Unloading of CO was normal, and there was no evidence of respiratory distress. Slight staining of the nares was seen. Postmortem examination revealed normal lungs and no evidence of irritation to the respiratory passages.

When the animals were removed from the chamber after exposure to smoke from fire-retarded polyurethane foam, seizures of varying degrees were evident. The frequency and severity of seizures increased; grand mal seizures were present by 1 hour after exposure. Seizures occurred earlier after exposure to smoke from the polyurethane foam with the higher concentration of fire retardant. All behavioral responses were severely impaired as a function of the frequency and severity of seizures. In the period immediately after exposure, the interval between seizures was marked by severe limitation of exploratory behavior, despite a significant amount of apparent voluntary motor activity at times. Lid-cornea and ear flick reflexes, elicited by probing with a cotton swab, were present. Response to pain was grossly diminished, with repeated pinpricks to the foot required to elicit a response. The righting reflex, tested by dropping the animal upside down from a height of about 30 cm, was present but impaired so that only the front paws were placed correctly.

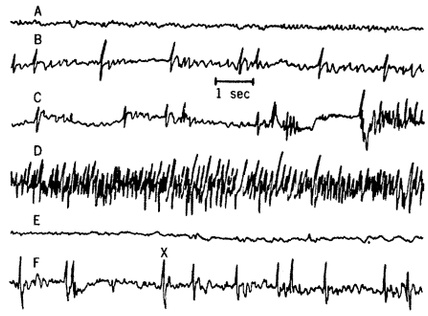


Fig. 1. An electroencephalogram recorded from a rat during exposure to smoke from the combustion of a fire-retarded polyurethane foam. These records were taken from an epidural electrode resting over an occipital lobe. Records are as follows: (A) control; (B) early epileptiform activity 10 minutes into exposure; (C) preseizure activity 14 minutes into exposure; (D) grand mal seizure activity 15 minutes into exposure (COHb, 6.4 percent; O_2Hb, 85 percent); (E) postictal activity; and (F) hyperexcitability demonstrated by the high amplitude "spike" (X) elicited with a single light flash.

The animal had a characteristic posture, sitting semicrouched with hind legs wide apart. Clusters of flexion jerks of sufficient force to lift the animal into the air occurred every 15 to 20 seconds. These jerks became more intense and culminated in a generalized motor seizure with tonic and clonic phases. Status epilepticus (repeated major motor seizures) finally ensued in approximately 1 hour. Purposeful behavior, such as sniffing in the air, pawing, or head nodding, occurred repetitively. These inappropriate automatisms were typical of psychomotor seizure activity. Aimless wandering occurred between seizures but when the seizures became more frequent, the animal was most often in a depressed postictal state.

After repeated major motor seizures, a froth appeared at the mouth; none was present during the early manifestation of seizure activity. There was no gross evidence of respiratory distress.

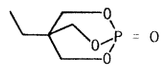
Postmortem examination of the tracheae, bronchi, and lungs revealed a serosanguinous froth present in varying amounts in larger passages and expressible from lung parenchyma. The lung surface was mottled, which indicated scattered hemorrhage. No gross evidence of pathology was found in the other organs.

To further define the toxic effects, samples of the fire-retarded foam were pyrolyzed in a 45-liter Plexiglas box in which a single rat was exposed. In addition to data obtained from blood removed through the intra-arterial cannula, recordings were made of the respiration rate, electrocardiogram, and electroencephalogram (EEG). Respiration records showed changes in breathing in response to smoke irritants, but no cardiac arrhythmia occurred. High amplitude spike discharges were seen in the EEG well before there were any visible signs of behavioral impairment

Table 2. A summary of the results of the behavioral assessment of rats after a 20-minute exposure to CO or to smoke from combustion of Douglas fir, from rigid-polyurethane foam, and from fire-retardant rigid-polyurethane foam. Abbreviations: ppm, parts per million; FR, fire retardant.

Material	COHb (%)	Time to move from 25-cm circle (sec)	Response to pain (pinprick)	Other comments
CO, 1500 ppm	38–53	12.4	Suppressed	
Wood, 5 g	30–46	11.4	Normal	Respiratory distress
Wood, 18 g	62	>60	None	Extreme respiratory distress All died within 24 hours
Foam, 0% FR	28–33	6	Suppressed	Normal behavior Slight staining of nares
Foam, 4% FR	23–26			One dead at end of exposure Focal seizures at end of exposure Grand mal seizures in 43 to 70 minutes No parasympathetic signs Normal CO unloading
Foam, 8% FR	5–6	>60	None	All animals showed myoclonic jerks which progressed to status epilepticus and death No parasympathetic signs

(Fig. 1). The spikes became more frequent and culminated in grand mal seizures. Analysis of a blood sample taken during a seizure showed 6 percent COHb (approximately the level expected in a heavy cigarette smoker). Chemical analysis (*6*) confirmed the presence of the bicyclic phosphate, 4-ethyl-l-phospha-2,6,7-trioxabicyclo[2.2.2.]octane-1-oxide (**1**) in the smoke.



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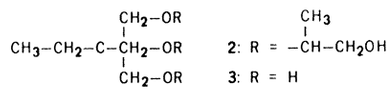
It is postulated by Voorhees *et al.* (*6*) that compound **1** is formed during the thermal decomposition of the urethane polymer by the production of the propoxylated trimethylolpropane adduct (**2**), which in turn decomposes to trimethylolpropane (**3**). Compound **3** is believed to further react with a reactive phosphorus species from the retardant additive to form compound **1**.



The chemical analyses were prompted by the similarities in the characteristics of intoxication of animals exposed to smoke from the fire-retarded foam and animals treated with intraperitoneal injections of the bicyclic phosphate compound **1** supplied by J. E. Casida (*7–9*). Homologous bicyclic phosphate compounds induce seizure activity in concentrations lower than 1 part per million (*7*). Compounds exhibiting such extreme toxicity could be present in biologically hazardous concentrations in a complex mixture (smoke) and be undetected by conventional analysis techniques such as gas chromatography and mass spectroscopy. This illustrates the necessity for a biological testing system to parallel chemical analytical methods during evaluation of a material's combustion products.

The sensitivity of a biological testing system should reflect the probable scenario of the fire hazard. The progressive loss of mental and behavioral functions followed by abnormalities in vital physiological functions leading to death is a typical sequence of impairment resulting from smoke intoxication. It is apparent from our observations that loss of behavior-dependent escape responses may occur well before lethal concentrations of "smoke" develop. The experimental approach of monitoring vital functions and behavior provides a biological testing system with an added level of sensitivity for the assessment of combustion products toxicity.

While our polyurethane foams are not commercial samples, the combination of ingredients is not uncommon in commercial formulations. This suggests that a major health hazard, independent of flame contact or CO intoxication, may be encountered by humans exposed to the combustion products of this class of materials during actual fires.

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Intestinal Metabolism of Phenacetin in the Rat: Effect of Charcoal-Broiled Beef and Rat Chow

Abstract. *The intestinal metabolism of phenacetin in vitro was increased 1100 percent in rats fed charcoal-broiled ground beef in a semisynthetic diet. The intestinal metabolism of phenacetin was increased 200 percent in rats fed a chow diet, as compared to rats fed the semisynthetic diet. The results obtained suggest a need for studies in man to determine whether charcoal-broiled meat and other dietary constituents can stimulate the intestinal metabolism of phenacetin or other drugs and thereby decrease their absorption and bioavailability.*

Recent studies showed that cigarette smoking enhances the metabolism, and lowers the plasma concentration, of orally administered phenacetin (*1*) in man without changing its plasma half-life (*2, 3*). These findings suggest that the enhanced metabolism of phenacetin in smokers may be occurring during the first pass through the liver, or in the gastrointestinal tract. Investigations in rats revealed the presence of an enzyme system in the wall of the small intestine which is capable of metabolizing phenacetin to *N*-acetyl-*p*-aminophenol (*3, 4*), and the results indicated that the activity of this enzyme system is increased in rats pretreated with cigarette smoke (*4, 5*); with 3,4-benzpyrene (*3, 5*), a constituent of cigarette smoke (*6*); or with 3-methylcholanthrene (*4*). Studies with everted sacs of rat small intestine, suspended in a phenacetin solution, were also made to determine whether changes in the intestinal metabolism of phenacetin may influence the amount of this drug that is absorbed unchanged into the bloodstream. These studies showed that an increase in phenacetin-metabolizing activity of the intestine decreased the amount of phenacetin and increased the amount of its metabolite, *N*-acetyl-*p*-aminophenol, that was transferred from the mucosal to the serosal side of the intestinal sac (*5*).

Because of the possibility that various substances normally present in man's diet may influence the intestinal metabolism and bioavailability of drugs, we have initiated studies on the effects of dietary constituents on the metabolism of phenacetin by the rat intestine. We now report a stimulatory effect of charcoal-broiled ground beef and of a rat chow diet on the metabolism of phenacetin by the rat small intestine.

Male Long-Evans rats (Blue Spruce Farms, Altamont, N.Y.), weighing 170 ± 10 g, were maintained on a Wayne Lab-Blox rat feed (Allied Mills, Chicago) diet. After arrival in our laboratory, the rats were fed freely a nutritionally complete semisynthetic diet consisting of vitamin-free casein, 27 percent; starch, 59 percent; vegetable oil, 10 percent; salt mixture, 4 percent; and a complete vitamin supplement (normal protein test diet, Nutri-