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Toxicity testing of fire effluents —

Part 5:
Prediction of toxic effects of fire effluents

Essais de toxicité des effluents du feu —

Partie 5: Prédictions concernant les effets toxiques des effluents du feu

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Foreword

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The main task of technical committees is to prepare International Standards, but in exceptional circumstances a technical committee may propose the publication of a Technical Report of one of the following types:

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Technical Reports of types 1 and 2 are subject to review within three years of publication, to decide whether they can be transformed into International Standards. Technical Reports of type 3 do not necessarily have to be reviewed until the data they provide are considered to be no longer valid or useful.

ISO/TR 9122-5, which is a Technical Report of type 2, was prepared by Technical Committee ISO/TC 92, *Fire tests on building materials, components and structures*, Sub-Committee SC 3, *Toxic hazards in fire*.

This document is being issued in the type 2 Technical Report series of publications (according to subclause G.4.2.2 of part 1 of the IEC/ISO Directives) as a "prospective standard for provisional application" in the field of toxicity testing of fire effluents because there is an urgent need for guidance on how standards in this field should be used to meet an identified need.

This document is not to be regarded as an "International Standard". It is proposed for provisional application so that information and experience of its use in practice may be gathered. Comments on the content of this document should be sent to the ISO Central Secretariat.

A review of this type 2 Technical Report will be carried out not later than two years after its publication with the options of: extension for another two years; conversion into an International Standard; or withdrawal.

ISO/TR 9122 consists of the following parts, under the general title *Toxicity testing of fire effluents*:

— *Part 1: General*

— *Part 2: Guidelines for biological assays to determine the acute inhalation toxicity of fire effluents (basic principles, criteria and methodology)*

— *Part 3: Methods for the analysis of gases and vapours in fire effluents*

— *Part 4: The fire model (furnaces and combustion apparatus used in small-scale testing)*

— *Part 5: Prediction of toxic effects of fire effluents*

Annexes A and B of this part of ISO/TR 9122 are for information only.

Toxicity testing of fire effluents —

Part 5:
Prediction of toxic effects of fire effluents

1 Scope

This part of ISO/TR 9122 reviews the progress of bioanalytical methodology, including the application of mathematical models which are available and may be used in the toxicological assessment of fire effluent atmospheres. Attention is also given to the application of such models as a means to minimize the use of laboratory animals in the testing of materials for fire effluent toxicity.

2 Background

A major thrust in the assessment of the toxic effects of fire effluents has been in the development of mathematical models for predicting such effects from appropriate data on the composition and concentrations of the fire gases. The objectives of these efforts are twofold. Assessment of smoke toxicity from analytical data could obviate much of the use of live animals in conventional bioassay methodology. Furthermore, providing that both qualitative and quantitative differences in toxicological effects between laboratory animals and man are understood, such modelling methodology can also be used for estimating the time to development of untenable conditions in either real or simulated fire scenarios.

The development of smoke toxicity modelling began in the late 1960's and continued into the 1970's, with concepts proposed by Y. Tsuchiya and K. Sumi at the National Research Council Laboratories in Canada[1 and 2]. A deterrent to its acceptability at that time was the widely-held perception that the toxicity of smoke could be as complex and as exotic as its composition. However, work in the United Kingdom by D.A. Purser and W.D. Woolley[3] demonstrated that smoke toxicity could, to a large extent, be explained both qualitatively and quantitatively in terms of a small number of important toxic gases. This provided support for the potential validity of smoke toxicity modelling. A publication in 1981 by S.C. Packham and G.E. Hartzell[4] together with the work of P.W. Smith[5], established a foundation for such modelling in the United States. Research in this area advanced considerably during the 1980's, such that more recent publications by G.E. Hartzell[6 to 8], B.C. Levin[9 and 10], D.A. Purser[11] and Y. Tsuchiya[12] set the stage for the development of toxic hazard modelling which takes into account combinations of toxic insults as they would occur in a fire.

3 General concepts

Basic to all the modelling techniques is some expression of the concentration of a toxicant relative to that concentration known to cause a particular toxic effect resulting from a given time of exposure. Lacking in some of the early development efforts was a clear concept of the "dose" of a toxicant, along with appreciation of its utility as a tool in modelling. Also lacking was a good base of toxicological data appropriate for short exposures to relatively high concentrations of toxicants. Additionally, there was insufficient understanding of relevant laboratory decomposition models upon which the toxicological modelling was to be based.

Quantification of "dose" has been fundamental to the development of methodology for modelling the toxicological effects of inhalation of fire gases, whether in laboratory animals or humans. Physiological responses are usually dose-related, i.e., the magnitude of the effect increases with increasing amounts or accumulated body burden of a physiologically active agent. Since the actual dose of toxicants from inhalation of fire effluents cannot be measured directly, the assumption is made that the dose is a function of fire effluent (or toxicant) concentration and exposure time[13]. This dose is really an expression of the insult to which a subject is ex-

posed. The term "exposure dose" is probably more accurate and has become the preferred term in combustion toxicology.

Concentrations of common fire gas toxicants, such as carbon monoxide and hydrogen cyanide, are usually expressed as parts per million by volume [ppm (*V*/*V*)]. Therefore, the exposure dose can be expressed as the product of the concentration, C, and time, t, (usually expressed in ppm·min). In the case of a changing concentration of a gaseous toxicant, the exposure dose is actually the integrated area under a concentration vs. time curve.

Often, the concentrations of fire gas toxicants are not known. In that event, one can still deal with the concept of exposure dose as it applies to smoke. Since smoke concentration cannot be quantified, an approximation is made that the smoke concentration is proportional to the mass loss during a fire. The integrated area under a mass loss per unit volume vs. time curve thus becomes a measure of smoke exposure dose (usually expressed in $g \cdot m^{-3} \cdot min$)[14 and 15]. (This concept of smoke exposure dose is described in ISO/TR 9122-2.) Smoke exposure dose at any point in time can be calculated from data obtained from a laboratory combustion device, instrumented experimental fires, data generated from mathematically modelled fires and even data estimated from real fires.

In order to model the toxic effects of exposure to fire effluents, it is necessary to obtain two basic pieces of information:

a) the exposure dose $C \cdot t$ generated by the fire (for the major toxic gases in the smoke or for the mass loss of the materials being combusted); and

b) the exposure dose $C \cdot t$ required for a given toxic effect (lethality or incapacitation).

Elementary approaches to estimation of toxic hazards can be based on simple mass loss per unit volume data, i.e. how much fire load is consumed and into what volume it has been dispersed. Recognizing that most materials typically exhibit 30 min LC_{50} values for their fire effluents in the range of approximately 30 $g \cdot m^{-3} \cdot min$[16], the US National Institute of Standards and Technology Hazard I Model uses a lethal tenability limit of 900 $g \cdot m^{-3} \cdot min$[17] if actual material data is unavailable. The British Standards Institution, somewhat more conservatively, employs a value of 500 $g \cdot m^{-3} \cdot min$[18]. These simple methods avoid the use of individual material LC_{50} values, which are not always known.

In the case of real fire scenarios, smoke transport, dilution and layering calculations can provide for estimation of smoke exposure doses presented at the breathing zone of subjects even in areas remote from a fire[17]. It is an important concept that "toxicological exposure doses" can be visualized as quantified entities that are generated from a fire, transported and then administered to exposed subjects.

4 Predictions involving one single fire gas

The simplest form of modelling involves the situation in which only one toxic fire gas is considered and where exposure doses associated with given effects, e.g. incapacitation or death, are constants for any exposure concentration (i.e. Haber's rule is valid and $C \cdot t = k$, where k is a constant exposure dose required for a given toxic effect). Unfortunately, this may not be the case over the range of concentrations of interest and it is desirable to determine the dependence of the effective exposure dose on the concentration of the toxicant. In practice it has been found that the exposure dose required to cause a particular response decreases with increasing concentration of a toxicant.

Numerous laboratory studies have involved the most prevalent gaseous fire effluents, i.e. CO, CO_2, O_2, HCN, HCl, HBr and NO_2, with exposure doses associated with lethality of rodents (mice, rats and guinea pigs) being reasonably well characterized. LC_{50} values from the literature are given in tables A.1 to A.6. With the inclusion of some limited data on macaque monkeys, baboons and humans, the data appear to suggest that, overall, the rat may be a reasonable model for humans with regard to lethality. (Sublethal effects, especially respiratory effects of irritants, are another matter, and the rat may not be an adequate model; however, some data are available for primates and humans.)

Once effective exposure doses are characterized, the concepts of the fractional exposure dose, along with the summation or integration of fractional exposure doses, result in workable tools in combustion toxicology[5 to 9, 11, 17 and 19]. Incremental exposure doses $C \cdot dt$ are calculated and related to the specific $C \cdot t$ exposure dose required to produce the given toxicological effect. Thus a fractional effective dose (FED) is calculated for each small time interval. Continuous summation of these fractional effective doses is carried out in order to calculate the accumulated exposure dose.

Mathematically, the model for an individual toxicant i can be expressed as:

$$\int_{t_0}^{t} \frac{C_i}{(C \cdot t)_i} \, dt \qquad \ldots (1)$$

Most toxicological modelling methodologies make use of this concept in one form or another.

5 Predictions involving multiple fire gases

There are two methods for predicting the toxic effects of fire effluent atmospheres containing multiple

toxicants. One is an empirical method involving mass loss measurements combined with toxic potency data of the material involved obtained from animal exposure data; the other is based upon analysis of the composition of the atmosphere in terms of the major known toxic products. The latter is then used to make predictions from the known effects of these gases and the interactions between them.

5.1 Use of mass loss measurements

This approach may be used to make assessments of the toxic effects, in particular lethality, of mathematically modelled fires, large scale experimental fires or real fire scenarios involving one or more materials.

For this method, it is necessary to determine the rate of mass loss of the materials in the fire, either by direct measurement or by mathematical modelling of fire growth and mass loss. The latter is based upon input data from small scale tests or other sources. The mass loss curve for the fire is then used in conjunction with toxic potency data for the specific materials as derived from small scale bioassay tests. The basic method for the determination of the toxic potency of the combustion products from individual materials is to perform a small scale combustion toxicity test on a material under conditions relevant to those in the fire and to find the lethal mass loss exposure dose (LCt_{50}) expressed in $g \cdot m^{-3} \cdot min$ or the equivalent. The mass loss curve for each material in the full scale fire is used to perform a fractional effective dose (FED) analysis in the same way as for a single gas as described previously. Where several materials are involved in a fire, the FEDs of each material are summed since, in practice, each material produces certain yields of the common major toxicants which are mixed together in the smoke. A number of practical and essentially similar methods for applying this approach have been published [8, 11, 17 and 18].

The advantage of this approach is its simplicity, since it requires a knowledge only of the mass loss concentration curve for the materials involved in the fire and the toxicities of those materials in terms of mass loss $C \cdot t$ products. It is robust in that, in practice, LCt_{50}s of many tested materials have been shown from small scale tests to fall into approximately one order of magnitude[11 and 16].

The disadvantages are that it normally only provides lethality information and does not allow for physiological deviations from ideal behaviour. It is also necessary to assume that lethal exposure doses in rats are similar to those in humans. Further, the method assumes that the toxicity of a material in a real fire will be the same as that in a small scale test. The last objection is probably the most serious limitation, but it can be overcome to some extent providing that care is taken that the small scale bioassay combustion toxicity tests on materials are conducted under conditions similar to those in the full scale fire. Thus, where toxic effects are being assessed for a fire that starts in the non-flaming mode and progresses through early flaming to become a large post-flashover fire, it will be necessary to use different lethal mass loss exposure doses for each stage of the fire.

5.2 Use of analyzed concentrations of major toxicants

This approach makes predictions of toxic effects based upon chemical analysis of the primary combustion products in the fire effluent along with knowledge of the toxic effects and toxic interactions of these products. It has two types of application. One is to replace or limit the use of animals in small scale bioassay combustion toxicity tests. If the lethal exposure dose to rodents for a particular test atmosphere from a material can be predicted from the measured atmosphere composition, then animal exposures can be avoided or used in a limited way to confirm the prediction. The other application is to make predictions of the likely incapacitating or lethal effects of exposure of humans to large scale or real fire atmospheres. This assumes a correlation between animal and human responses.

The full consequences of exposure to atmospheres containing multiple toxicants have only recently been examined in detail. Toxic fire gases may be classified into two main types, those whose main effect is to cause tissue hypoxia by impeding the delivery or use of oxygen in the tissues (carbon monoxide, hydrogen cyanide and low oxygen hypoxia) and those that are irritant, causing pain and tissue damage upon contact with the eyes and respiratory tract epithelium (principally organic irritants and acid gases). In addition to these, carbon dioxide is important, particularly due to its effects on respiration. A final class may be assigned as "unusual" toxicants.

Since the main fire gases within each class exert similar physiological effects through related mechanisms, it is not surprising that they are basically additive in their overall effects. What is now emerging is that, although these main classes of gases exert rather different physiological effects through different mechanisms, when all are present in mixtures, each can result in a certain degree of compromise experienced by an exposed subject and these effects are roughly additive in contributing to incapacitation or death. It should not be unexpected that varying degrees of a partially compromised condition may be roughly additive, since an examination of the physiological mechanisms whereby these toxicants exert their effects reveals a number of possible interactions, and these effects have been demonstrated in a number of studies. This principle of additivity is a key element in the assessment of toxicity from analytical data.

One of the reasons for these interactions, and a further complication with combined toxicants which is

more difficult to deal with, is that an individual toxicant may have physiological effects other than those of its principal specific toxicity. One obvious and very important effect is when toxicants affect respiration. Hydrogen cyanide causes hyperventilation, with up to four-fold increases in ventilation (respiratory minute volume RMV) being reported for monkeys early in an exposure[20]. This hyperventilation in primates (which eventually slows as narcosis results) can result in faster incapacitation from HCN itself than would otherwise be expected, along with more rapid uptake of CO and formation of carboxyhaemoglobin (COHb), should CO also be present. Similarly, carbon dioxide, although relatively innocuous itself at concentrations of up to 5 %, is a powerful respiratory stimulant causing an approximate doubling of respiration at a concentration of 3 % to 4 % and trebling of respiration at 5 % to 6 %[11]. This increases the rate of uptake of any other toxicants present approximately in proportion to the increase in ventilation. The inhalation of irritants also affects respiration and thereby can affect the uptake of asphyxiant gases. Although in the rat, respiratory depression resulting from HCl inhalation can slow the uptake of CO[21], inhalation of irritants such as HCl by primates tends to cause an increase in RMV[3]. Lung function changes are induced which appear to impair oxygen uptake into the blood[22], thereby potentially adding to the hypoxic effect of inhaled narcotic gases.

Allied to these respiratory effects is the development of acidosis. Evidence is emerging that metabolic acidosis, resulting from tissue hypoxia induced by gases such as CO and HCN, combined with respiratory acidosis caused by inhalation of CO_2, or stagnant hypoxia induced by irritants, can result in toxic effects not obviously predictable from the effects of the individual gases[9, 23 and 24]. With all these effects possible in the inhalation of mixtures of toxicants in real fire effluents, the situation is extremely complex. Very little research using toxicant combinations has been conducted using primates and the full extent of the combined effects on incapacitation and death of humans exposed to fire gas combinations is not yet fully understood.

In spite of the complexity of dealing with atmospheres containing multiple toxicants, considerable progress has been made in confirming and quantifying some of these effects from studies with rodents. For example, it is now well established that carbon monoxide and hydrogen cyanide are additive when expressed as fractional exposure doses required to cause a toxic effect[7, 9 and 10]. This effect has also been reported for dogs and primates[25 and 26]. Thus to a reasonable approximation, the fraction of an effective exposure dose of CO can be added to that of HCN in estimating the presence of a hazardous condition. When low oxygen is added to either or both of these hypoxic gases, there is evidence that a further additive effect occurs based on studies in rodents[9, 27 and 28] and humans[29]. The effect of CO_2 in increasing the rate of uptake of other toxic gases has already been mentioned, but apart from this, it is a narcotic in its own right at concentrations above 5 %, causing impairment or loss of consciousness in humans. Increased incidence of lethality (particularly postexposure), has been observed with certain combinations of CO and CO_2[23], possibly associated with the combined insults of respiratory acidosis (from the CO_2) with metabolic acidosis (caused by the CO), a condition from which the rodent has difficulty recovering postexposure. Other studies with rats involving CO_2 have shown combinations of CO_2 and NO_2 to exhibit synergism[24].

In the case of mixtures of hypoxic gases and an irritant gas (hydrogen chloride), analysis of the toxicological data shows that exposure doses leading to lethality of rats can also be additive[21 and 30]. Although not yet confirmed with primates, these studies imply that hydrogen chloride can be much more dangerous than previously thought when in the presence of carbon monoxide (and vice versa). A rapid respiratory acidosis was seen in the blood of rats exposed to HCl which, when coupled with the metabolic acidosis produced by the CO, resulted in severely compromised animals. It is also possible that in humans impairment of oxygen uptake into the blood occurs as a result of ventilation perfusion changes caused by inhalation of irritants. This can also be additive with the hypoxic effects of CO and other gases. These effects can have significance with regard to human fire exposures, impairing escape capability and leading to a prolonged hypoxaemia following rescue. The importance of these phenomena to humans is supported by evidence that the incapacitating effects of carbon monoxide can be enhanced in primates upon simultaneous exposure to HCl, the presence of which causes the partial pressure of oxygen in the arterial blood to be decreased[22]. This is presumably the case with other irritants as well. It has been observed that there can also be additivity of fractional effective doses between HCl and HCN[30]. Particularly striking was the incidence of postexposure deaths from concentrations of the toxicants, each of which alone would not be expected to result in any postexposure lethality. Deaths often occurred several days after exposure.

Interactions between multiple combinations of fire effluent toxicants have been particularly well studied using mice, by T. Sakurai at the Research Institute of Marine Engineering, Higashimurayama, Japan[27]. In general, these studies confirmed the effects reported and predicted by other investigators, giving additional confidence to predictive modelling by the methodology described.

A current limitation on the predictive power of gas combination toxicity models is in the area of irritancy. Only a small number of irritant chemicals are routinely measured in smoke, although at least twenty have been identified. There is also evidence that smoke is more irritating in practice than would be predicted

from even a comprehensive analysis of its composition, so that other factors, in addition to simple chemical toxicity, are possibly involved[11]. Two that have been identified as important are the irritant effects of particulate matter (soot) carrying adsorbed toxicants deep into the lung and the possible role of free radicals in smoke in causing deep lung damage[11]. These areas require further investigation in order to improve the predictive power of models. Currently, the only way that smoke irritancy can be factored into models is to use data on irritancy from small scale bioassay tests. It is to be hoped that following further research on the toxicity of important irritants, as well as improved chemical analysis of combustion product atmospheres, it will be possible to predict these effects as effectively as those of hypoxic gases can now be predicted.

6 Fractional effective dose models

6.1 Mass loss models

The development of toxic conditions and estimates of toxic hazard in full scale fire scenarios can be made from mass loss (mass burned) concentration-time profiles and toxic potency data for the materials involved. The justification for this approach is based upon the demonstrated additivity of fractional effective doses (FEDs) of many of the individual toxic gases in fires.

6.1.1 Hartzell-Emmons mass loss FED model

Using this concept, an FED model using mass loss toxicity data for individual materials has been developed[8]. The FED model takes the form of expression (2) for n materials. The total fractional effective exposure dose at any time, t, would be:

$$\sum_{i=1}^{n} \int_{t(b_i)}^{t} \frac{C_i - b_i}{K_i} \, dt \qquad \ldots (2)$$

where

C_i represents smoke concentration (from mass burning rate data);

K_i and b_i characterize the toxicity of component i. The values for K_i and b_i are respectively the slope and intercept of a plot of LC_{50} vs. 1/time-of-exposure for component i.

In order to prevent "negative doses" from accumulating when C_i is less than b_i, the lower limit for the integration is the value of t_i when C_i is equal to b_i. The time at which expression (2) becomes unity (100 %) is the time of exposure which would be expected to result in 50 % effect. Computer programs, using a variety of fire scenarios and material input data, have been developed for assessing potential toxic hazard for fires involving several materials simultaneously.

6.1.2 Purser mass loss FED model

A similar model has been proposed by Purser which also relies upon knowledge of mass loss burning rate and dispersal volume[11]. A simple, elementary calculation makes use of a single average mass loss exposure dose for lethality for all materials of 300 $g \cdot m^{-3} \cdot min$. For more advanced calculations, use is made of LCt_{50} data for individual materials obtained under conditions relevant to the fire condition being modelled (non-flaming, early flaming or post-flashover).

6.1.3 British Standards Institution mass loss FED model

A third, and quite similar model has been published by the British Standards Institution[18]. This model also relies on knowledge of the mass loss burning rate for each material in the fire and the volume into which the products are dispersed. Individual materials are allocated toxic potency factors relative to wood (derived from small scale LCt_{50} data) for input into the calculation.

6.1.4 National Institute of Standards and Technology (USA) Hazard I model

The tenability (TENAB) routine used in the Hazard I computer program allows the utilization of a mass loss rate model, with input supplied by the Fire and Smoke Transport (FAST) part of the model[17]. FAST is a program which calculates the evolving distribution of smoke and fire gases and the temperature throughout a building during a fire. FAST essentially solves a set of equations that predict the change in the energy (and thus temperature) and mass (and thus the smoke and gas concentrations) over small increments of time. The changing exposure of an occupant moving through the building or overtaken by the descending layer are accounted for by adding (integrating) these concentrations over time in TENAB. For example, an occupant is initially exposed to the lower layer until the interface reaches head height. The time that this occurs is obtained from the interface position data for that room. Thus, the exposure at any time equals the accumulated $C \cdot t$ value up to that time. When moving from room to room, the accumulated exposure dose for each room is computed. The total exposure is the sum of the exposure doses accumulated in each room until the occupant exits the building. In the absence of other information, all materials, are assumed to have LCt_{50} values of 900 $g \cdot m^{-3} \cdot min$. Other values can be chosen by the program operator in order to address incapacitation, for example.

6.2 Toxic gas models

These methods all depend upon knowledge of the composition of a combustion product atmosphere as a function of time during a fire or fire test, and of the

toxic effects of the various combustion product combinations. Although there are a very large number of toxic products in fire atmospheres, the finding that a relatively small number are most important enables models based upon this concept to be used. They are all based upon the concept that the fractional exposure doses for each gas are primarily additive. The development of toxic conditions or toxic hazard in a fire or fire test may therefore be estimated from the concentration-time profiles of the combination of the individual toxicants.

The majority of these methods, based upon rat lethality data, are particularly useful for predicting the lethality of chemically analyzed atmospheres in small scale tests. They enable the principle of toxic gas additivity, along with more subtle interactions, to be tested experimentally. They enable first approximation predictions of the toxic effects of combustion products from materials under different decomposition conditions. The methods can also reduce the need for animal experiments, but when used in conjunction with animal exposures, it is possible to determine to what extent the toxicity of the combustion products from materials can be explained in terms of the known toxicants. To the extent that lethal exposure doses in the rat are similar to those in humans, which is considered to be approximately the case, it is also possible to make some predictions about the possible human lethal exposure hazard in large scale fires where measurements of the major toxicant concentrations have been made.

6.2.1 Hartzell-Emmons toxic gas FED model

The fractional effective dose model of Hartzell-Emmons[8] was originally developed for modelling the additive lethal effect to rats of gases in combination in small scale tests. The model has so far been limited to experimental data for CO, HCN and HCl; however, it could easily be extended to include low oxygen hypoxia and any other measured toxicants. The basic expression for the FED model is the same as expression (2) except that i represents individual gases rather than smoke from products. The values of K_i and b_i are respectively the slope and intercept of a plot of LC_{50} vs. the reciprocal of the time of exposure for each toxic gas considered.

Although data for doing so are limited, the model is theoretically capable of predicting LC_{50} values in the testing of many materials for the toxicity of their fire effluents. This is done by measuring toxic gas concentrations as a function of time over a range of material mass loss values. The model is then used to estimate the mean time of exposure for each mass loss value which would be expected to cause lethality, with the approximation that each such mass loss value represents the LC_{50} for that exposure time. From the developed relationship between mass loss and exposure time to cause 50 % lethality, the LC_{50} for any time of exposure can be calculated. One reported example, based only on CO and HCN, gave a predicted 30 min LC_{50} value for a material of 11,4 $g \cdot m^{-3}$, in excellent agreement with 10,5 $g \cdot m^{-3}$ determined using biossay methods[7].

6.2.2 National Research Council (Canada) model

The basic FED concept, expressed somewhat differently, can also take the form,

$$a\int_{t_0}^{t}[C(t-t^0)-C^0]dt \quad \ldots (3)$$

where

C^0 is a threshold concentration of the toxicant;

t^0 is the minimum time for a toxicological effect to occur; and

a is a constant specific to the toxicant[12].

As with the FED model, constants are determined from a concentration-time-response database for the toxicant. Agreement between the two methods described for prediction of incapacitation or death of rats exposed to either CO or HCN is surprisingly good.

The NRC model for predicting toxicological effects of individual fire gases has also been expanded to handle multiple component mixtures. The mathematics become very complex and application of the model for this purpose has not been practised.

6.2.3 National Institute of Standards and Technology (USA) N-gas model

Another approach to toxicological interactions between common fire gases is that of the N-gas model[9]. The N-gas model is based upon studies of the lethal interactions in rats of up to five gases (CO, CO_2, HCN, HCl and low O_2)[31]. A form of the FED model, it uses the time-integrated average concentrations of individual gases in cases where concentrations change over time. It is used largely for 30 min exposures to constant concentrations; however, other exposure times have been used. The main usefulness of the method is to predict LC_{50} values from the analytical results of small scale materials tests or smoke samples taken from large scale tests and to determine the extent to which rat lethality can be explained in terms of the four common gases.

Equation (4) has been experimentally derived to predict the death of 50 % of exposed rats either within an exposure or within a 24 h postexposure period for the four gases:

$$\frac{m\phi_{CO}}{\phi_{CO_2}-b}+\frac{\phi_{HCN}}{LC_{50,\,HCN}}+\frac{21-\phi_{O_2}}{21-LC_{50,\,O_2}}\approx 1 \quad \ldots (4)$$

where

ϕ_{CO} is the concentration of CO, expressed in parts per million by volume;

ϕ_{CO_2} is the concentration of CO_2, expressed as a percentage by volume;

ϕ_{HCN} is the concentration of HCN, expressed in parts per million by volume;

ϕ_{O_2} is the concentration of O_2, expressed as a percentage by volume;

m and b are respectively the slope and intercept of the interactive curve of CO and CO_2 which depicts the increasing toxicity of CO as CO_2 concentration increases up to 5 %.

The LC_{50} values of the individual gases will change depending on the exposure times. For a 30 min exposure, $LC_{50,CO}$ equals 6 600 ppm (V/V); $LC_{50,HCN}$ equals 160 ppm (V/V) for deaths occurring within a 30 min exposure or 110 ppm (V/V) for deaths occurring during a 30 min exposure plus a subsequent 24 h postexposure observation period; 50 % of the animals die in 30 min when ϕ_{O_2} equals 5,4 %. m and b equal -18 and 122 000, respectively, if the CO_2 concentrations are 5 % or less; and 23 and -39 000 respectively, if the CO_2 concentrations are above 5 %. The period under consideration here is restricted to 24 h. A more recent version of the N-gas model also includes a term for incorporating the postexposure lethality of rats due to the pulmonary irritant effects of HCl[31]. The term is based on a series of LC_{50} values for HCl for various exposure times (see table A.3), with the 30 min LC_{50} being most commonly used.

Since the concentration-response curves for animal deaths from combustion products are very steep, the assumption is made that if any percentage of the animals die (not including 0 or 100 %), the concentration should be close to the LC_{50} value. Examination of a series of pure gas experiments in which various percentages of the animals died indicated that the mean N-gas value was 1,07 with 95 % confidence limits of 0,20[19]. Deaths below this range may then be attributed to the additional toxicity contributed by other gases or factors. Above this range, all the animals would be expected to die.

The N-gas model has value in indicating the extent to which the lethal toxic potency of a fire effluent atmosphere is due to the four common gases and, thereby, can be used to minimize animal exposures in small scale tests and to detect situations where materials produce combustion products with unusual toxic potency.

A variant of the N-gas equation has been developed for use in the tenability (TENAB) routine of the National Institute of Standards and Technology Hazard I model[17]. This gives Hazard I the capability of handling concentrations of mixtures of fire gases over time increments.

6.2.4 Human incapacitation model

This model, also based on FED concepts, is applied to actual physiological uptake functions and to effects of the major toxic fire gases[11]. It is designed to predict toxic hazard in terms of exposure dose and time to incapacitation for humans in fires and is intended for use in fire engineering calculations of modelled fire scenarios, full scale fire tests and data related to real fire victims. Like all the multiple toxicant models, it relies on measured or calculated concentration-time data for the important toxic fire gases. Potentially, it is possibly the most sophisticated of models, making use of known physiological reactions of humans to CO, CO_2, HCN, oxygen vitiation, irritants and even heat and smoke obscuration. The FED equations developed for the model are derived primarily from experimental data obtained with humans and primates.

The major strengths of the model lie in its treatment of the major hypoxic fire gases, CO, HCN, low oxygen and CO_2, and also its treatment of radiant and convected heat and smoke obscuration. It shares the limitations of the other models with regard to irritants. The model treats hypoxic and irritant effects as separate, whereas recent work has shown that irritants also add to the hypoxic insult in fires. Apart from this, the irritant effects of common acid gases such as HCl or HF can be modelled in terms of their sensory irritant and lung irritant effects. Sensory irritancy is treated as concentration related, while lung irritancy (inflammation and oedema) is treated as dose related. For the majority of fire atmospheres, which contain a mixture of organic and acid gas irritants, irritancy is modelled in terms of mass loss exposure concentration and dose. A mass loss concentration of 1,0 $g \cdot m^{-3}$ is considered to produce a degree of incapacitation due to sensory irritation and an accumulated exposure dose of 300 $g \cdot m^{-3} \cdot min$ is considered likely to cause serious postexposure lung inflammation.

The complexity of the physiological model requires one to consult the literature for details; however, the model can be summarized as follows:

a) CO and HCN are considered to be directly additive.

b) CO_2 increases the rate of uptake of CO and HCN in proportion to its effect on the RMV.

c) The narcotic hypoxic effect of low oxygen hypoxia is considered to be directly additive to the combined effects of CO and HCN.

d) The narcotic effects of CO_2 above 5 % concentration is considered to act independently of the effects of the other gases.

e) Fractional exposure doses of HCN and low oxygen hypoxia are concentration and time dependent, while the dose of CO causing incapacitation is considered to be independent of time for periods of up to 1 h.

f) Irritancy acts independently of hypoxic narcosis. (Adjustments of the model to accommodate such interaction are under development, however.)

Based on these principles, it is possible to derive a fractional incapacitating dose (FID) equation for hypoxic narcosis as follows:

$$FI_N = [(FI_{CO} + FI_{HCN})V_{CO_2} + FI_O] \quad \ldots (5)$$

or

$$FI_N = [(FI_{CO} + FI_{HCN})V_{CO_2} + FI_{CO_2}] \quad \ldots (6)$$

where

FI_N fraction of an incapacitating exposure dose of all narcotic gases;

FI_{CO} fraction of an incapacitating exposure dose of CO;

FI_{HCN} fraction of an incapacitating exposure dose of HCN;

V_{CO_2} multiplication factor of CO_2-induced hyperventilation;

FI_O fraction of an incapacitating exposure dose of low oxygen hypoxia; and

FI_{CO_2} fraction of an incapacitating exposure dose of CO_2.

For a 1 min exposure to each gas, the following expressions may be used:

$$FI_{CO} = \frac{8{,}292\,5 \times 10^{-4}\ \phi_{CO}^{1{,}036}}{30} \quad \ldots (7)$$

$$FI_{HCN} = \frac{1}{\exp(5{,}396 - 0{,}023\ \phi_{HCN})} \quad \ldots (8)$$

$$V_{CO_2} = \frac{\exp(0{,}190\,3\ \phi_{CO_2} + 2{,}000\,4)}{7{,}1} \quad \ldots (9)$$

$$FI_O = \frac{1}{\exp[8{,}13 - 0{,}54(20{,}9 - \phi_{O_2})]} \quad \ldots (10)$$

$$FI_{CO_2} = \frac{1}{\exp(6{,}162\,3 - 0{,}518\,9\ \phi_{CO_2})} \quad \ldots (11)$$

where

ϕ_{CO} is the concentration of CO, expressed in parts per million by volume;

ϕ_{CO_2} is the concentration of CO_2, expressed as a percentage by volume;

ϕ_{HCN} is the concentration of HCN, expressed in parts per million by volume;

ϕ_{O_2} is the concentration of O_2, expressed as a percentage by volume.

Having calculated the effects of the narcotic fire gases, steps are then taken to assess the effects of radiant and convected heat, smoke obscuration and sensory and lung irritation. In the human incapacitation model, sensory irritation, radiant heat and smoke obscuration are treated as threshold values which, if exceeded, would indicate that hazardous conditions capable of causing some degree of incapacitation would exist. Lung irritation, convected heat and the effects of hypoxic gases are considered to be accumulated in the form of fractional exposure doses, but each is treated as acting independently such that incapacitation is predicted when the FED of any one of these factors reaches unity. Death is considered likely to occur when any of the factors reaches an FED of approximately 2.

The human incapacitation model may be simplified by using the following approximation to FI_{CO} for 1 min exposures to CO:

$$FI_{CO} = \frac{\phi_{CO}}{25\ 000} \quad \ldots (12)$$

where ϕ_{CO} is the concentration of CO, expressed in parts per million by volume.

FIDs for 1 min exposures to low oxygen and HCN for different exposure concentrations are given in table 1.

Table 1

O_2 %	FI_O	HCN ppm (V/V)	FI_{HCN}
21 to 13	0	0 to 50	0
13 to 12	0,02	50 to 100	0,05
12 to 11	0,05	100 to 125	0,10
11 to 10	0,08	125 to 150	0,15
10 to 9	0,15	150 to 175	0,25
9 to 8	0,25	175 to 200	0,50
8 to 7	0,40	200	1,00
7 to 6	0,70		

The multiplication factor for hyperventilation induced by CO_2 is shown in table 2.

Table 2

CO_2 concentration, ϕ_{CO_2} %	Hyperventilation multiplication factor, V_{CO_2}
0 to 2	1,0
2 to 3	1,5
3 to 4	2,0
4 to 5	2,5
5 to 6	3,0
6 to 7	3,5
7 to 8	4,5
8 to 10	4,8

A mass loss concentration of 1 $g \cdot m^{-3}$ is considered to cause sufficient sensory irritation to result in incapacitation, while a mass loss exposure dose of 300 $g \cdot m^{-3} \cdot min$ is considered capable of causing severe postexposure lung inflammation.

7 Conclusions

Methodology for the prediction of the toxic effects of fire effluents has made considerable progress, but is still very much in a developmental stage. Several models have been developed, each with some reasonably credible applications but each still with considerable limitations. The reader is directed to the original literature for detailed examples and illustrations of the models. Most often limiting has been the availability and quality of input data. As yet, fire growth models are not capable of predicting concentration-time profiles of toxicants; neither are such data generally available from published reports describing full scale fire tests.

In common among all the methodologies are the concepts of the accumulation of exposure doses of toxicants and of the additivity of toxicological effects for most tested gases, each toxicant taking its toll of an exposed subject in its own way, as it contributes to the overall insult. (An exception may be the effects of sensory irritation, which are not dose related, even though different sensory irritants may, themselves, be considered additive.)

The models, differing somewhat in the input data required and in their application, are of two types: those based upon empirically derived mass loss toxicity data and those based upon measured, but often changing, concentrations of known toxicants in the smoke.

The main advantage of the mass loss models is that they can be simply applied to either small or large scale fires providing that the input data, in the form of mass loss for the materials involved, dispersal volume and rat lethality exposure dose data, are available for the materials involved. All four models should give very similar numerical answers if run with the same input data. It should be emphasized that they all assume that lethal doses to humans will be the same as those to rats.

Of the toxic gas concentration models, the FED model is a powerful method for predicting rat lethality in either small or large scale fire tests, particularly where the concentrations of the gases considered change with time. It has, therefore, the potential capability of predicting LC_{50} values in the testing of many materials for the toxicity of their fire effluents. The model can also be used to predict the development of conditions hazardous to human life, assuming a relationship to rat lethality. The N-gas model can be useful for predicting rat lethality from the five gases considered. Lack of confirmation with animal exposures can thus reveal the potential existence of other toxic effects. The human incapacitation model, designed specifically for prediction of incapacitation hazards in humans, uses rodent sensory irritation and lethality data only for the assessment of irritancy. The model, therefore, does not apply to the testing of materials in the laboratory and to the potential reduction of the use of animals for such testing. However, to a large extent, it replaces the need for such tests. Where rat lethality and human incapacitation models are extrapolated to make predictions of lethality in humans, there should be reasonable agreement between the results.

Each model has its own particular utility, depending upon the input data available and the objective desired. When predictive modelling is applied to specific fire scenarios, it is often desirable to use elements of more than one model. When available, use should be made of both mass loss and toxic gas concentration data. Selection and appropriate use of a predictive model should be under the guidance of an expert professional skilled in the various techniques. Although modelling methodology has advanced significantly, considerable judgement is still required in the current state-of-the-art of predicting the toxic effects of fire effluents.

Annex A
(informative)

Lethal toxic potency tables for fire effluent toxicants

Lethal toxic potency (LC_{50}) values are statistical calculations and are always associated with confidence limits, usually 95 %. In the interest of simplifying the following tables, the confidence limits are not shown.

Serious users of these data should consult the literature for the confidence limits, as well as for more complete description of the experimental details.

Table A.1 — Lethal toxic potencies of carbon monoxide

LC_{50} values in ppm (V/V)

Exposure time min	Rats	Mice	Guinea pigs	Monkeys[1]	Humans[1]
1	107 000 [2]				
2	42 500 [2]				
5	14 000 [2]			6 000 to 8 000 [3], [4]	6 000 to 8 000 [3], [4]
10	9 800 [2]				
20	7 400 [2]				
30	6 600 [2]	3 570 [5]	17 500 [6]	900 to 1 000 [3], [4]	1 000 to 2 000 [3], [4]
	6 400 [7]	3 500 [8]			
	5 000 to 6 000 [9]				
	5 500 [3]				
	5 275 [10]				
60	4 900 [2]				

1) These values are for incapacitation of a subject engaged in light activity. It is estimated that death is likely at approximately twice these concentrations.

2) Levin: see reference [32].

3) Kimmerle: see reference [33].

4) Purser: see reference [34].

5) Hilado: see reference [35].

6) Hartzell: see reference [36].

7) Hartzell: see reference [21].

8) Alarie: see reference [37].

9) Herpol: see reference [38].

10) Lynch: see reference [39].

Table A.2 — Lethal toxic potencies of hydrogen cyanide

LC_{50} values in ppm (*V*/*V*)

Exposure time min	Rats	Mice	Guinea pigs	Primates/humans	
				Incapacitation	Death[1]
1	3 000 [2]				
2	1 600 [2]				
5	570 [2]			150 to 200 [3], [4]	250 to 400 [5]
10	290 [2]	166 [6]			
20	170 [2]				
30	110 [2]		201 [7]	90 to 120 [3], [4]	170 to 230 [5]
	160 [8]				
	170 [9]				
	142 [10]				
	200 [11]				
	157 [12]				
	116 [13]				
60	90 [2]				

1) These values are not LC_{50}s, but are estimates based on available data.
2) Levin: see reference [32] — includes 24 h postexposure.
3) Kimmerle: see reference [33].
4) Purser: see reference [40].
5) Purser: see reference [40].
6) Alarie: see reference [37].
7) Hartzell: see reference [36] — includes 24 h post exposure.
8) Levin: see reference [32] — within exposure only.
9) Hartzell: see reference [6] — within exposure only.
10) Kimmerle: see reference [33].
11) Kimmerle: see reference [33].
12) Yamamoto: see reference [41] — within exposure only.
13) Lynch: see reference [39] — includes 24 h postexposure.

Table A.3 — Lethal toxic potencies of hydrogen chloride

LC_{50} values in ppm (*V/V*)

Exposure time min	Rats	Mice	Guinea pigs	Primates/humans[1]
5	15 900 [2]	13 745 [3]		17 000
10	8 370 [2]	10 138 [4]		
15	6 920 [2]		2 900 [5]	10 000
22,5	5 920 [2]			
30	3 800 [2]	2 644 [3]	1 350 [5]	5 000
60	2 810 [2]			

1) These values are not LC_{50}s, but estimates based on conditions of animals after exposure. The 5 min exposure resulted in postexposure deaths[45]. The 15 min and 30 min exposures yielded subjects that survived indefinitely[42].

2) Hartzell: see reference [42] — includes 14 d postexposure.

3) Darmer: see reference [43] — includes 7 d postexposure.

4) Alarie: see reference [44] — includes 3 h postexposure.

5) Hartzell: see reference [36] — includes 14 d postexposure.

Table A.4 — Lethal toxic potencies of "low oxygen hypoxia"

LC_{50} values in % (*V/V*)

Exposure time min	Rats	Mice	Guinea pigs	Primates/humans	
				Incapacitation	Death[1]
5	4,0 [2]				
10	4,8 [2]				
20	5,2 [2]				
30	5,4 [3]	6,7 [4]		9,5 to 12 [5], [6]	7 to 9,5 [5], [6]
60	5,8 [2]				

1) These values are not LC_{50}s, but are estimates based on available data.

2) Levin: see reference [45].

3) Levin: see reference [46].

4) Alarie: see reference [37].

5) Kimmerle: see reference [33].

6) Purser: see reference [47].

Table A.5 — Lethal toxic potencies of nitrogen dioxide

LC_{50} values in ppm (V/V)

Exposure time min	Rats	Mice	Guinea pigs	Primates/humans[1]
5	831 [2]	1 880 [2]		
30	127 [3]	204 [4]		
	200 [5]			
30 to 60				100 to 200 [2]

1) These values are not LC_{50}s, but are estimates based on available data.
2) Kimmerle: see reference [33].
3) Hartzell: see reference [48] — includes 14 d postexposure.
4) Alarie: see reference [44].
5) Levin: see reference [24] — includes 14 d postexposure.

Table A.6 — Lethal toxic potencies of hydrogen fluoride

LC_{50} values in ppm (V/V)

Exposure time min	Rats	Guinea pigs	Primates
15		4 327 [1]	
30	2 042 [1], [2]		
	3 500 [3]		
60	2 240 [4]		1 774 [5]
	2 340 [6]		
	1 395 [7]		

NOTE — All LC_{50}s based on exposure plus 14 d observation period.

1) Rosenholz: see reference [49].
2) Hilado: see reference [50].
3) Darmer: see reference [51].
4) Valentine: see reference [52] — in dry air.
5) MacEwen: see reference [53].
6) Valentine: see reference [52] — in humid air.
7) Wohlslagel: see reference [54].

Annex B
(informative)

Bibliography

[1] TSUCHIYA, Y. and SUMI, K., Thermal Decomposition Products of Polyvinyl Chloride, *J. Applied Chemistry,* **17**, p. 364, 1967.

[2] TSUCHIYA, Y. and SUMI, K., Evaluation of the Toxicity of Combustion Products, *J. Fire and Flammability,* **3**, pp. 46-50, 1972.

[3] PURSER, D.A. and WOOLLEY, W.D., Biological Studies of Combustion Atmospheres, *J. Fire Sciences,* **1**, No. 2, pp. 118-144, 1983.

[4] PACKHAM, S.C. and HARTZELL, G.E., Fundamentals of Combustion Toxicology in Fire Hazard Assessment, *J. Testing and Evaluation,* **9**, No. 6, p. 341, 1981.

[5] SMITH, P.W. *et al.,* Effects of Exposure to Carbon Monoxide and Hydrogen Cyanide, *Proceedings of International Symposium on Physiological and Toxicological Aspects of Combustion Products,* Salt Lake City, UT, March, 1974; National Academy of Sciences, Washington, D.C., 1976.

[6] HARTZELL, G.E. *et al.,* Modeling of Toxicological Effects of Fire Gases: II. Mathematical Modeling of Intoxication of Rats by Carbon Monoxide and Hydrogen Cyanide, *J. Fire Sciences,* **3**, No. 2, pp. 115-128, 1985.

[7] HARTZELL, G.E., SWITZER, W.G. and PRIEST, D.N., Modeling of Toxicological Effects of Fire Gases: V. Mathematical Modeling of Intoxication of Rats by Combined Carbon Monoxide and Hydrogen Cyanide Atmospheres, *J. Fire Sciences,* **3**, No. 5, pp. 330-342, 1985.

[8] HARTZELL, G.E. and EMMONS, H.W., The Fractional Effective Dose Model for Assessment of Hazards Due to Smoke from Materials, *J. Fire Sciences,* **6**, No. 5, pp. 356-362, 1988.

[9] LEVIN, B.C. *et al.,* Effects of Exposure to Single or Multiple Combinations of the Predominant Toxic Gases and Low Oxygen Atmospheres Produced in Fires, *Fundamental and Applied Toxicol.,* **9**, pp. 236-250, 1987.

[10] LEVIN, B.C. *et al.,* Toxicological Effects of the Interactions of Fire Gases and Their Use in a Toxic Hazard Assessment Computer Model, *The Toxicologist,* **5**, p. 127, 1985.

[11] PURSER, D.A., Toxicity Assessment of Combustion Products and Modeling of Toxic and Thermal Hazards in Fire, *SFPE Handbook of Fire Protection Engineering,* National Fire Protection Association, Quincy, Massachusetts, Section 1, pp. 200-245, 1988.

[12] TSUCHIYA, Y. and NAKAYA, I., Numerical Analysis of Fire Gas Toxicity: Mathematical Predictions and Experimental Results, *J. Fire Sciences,* **4**, No. 2, pp. 126-134, 1986.

[13] MACFARLAND, H.N., Respiratory Toxicology, *Essays in Toxicology,* **7**, W. Hayes, Jr., Ed., Academic Press, Chapter 5, pp. 121-154, 1976.

[14] ALEXEEFF, G.V. and PACKHAM, S.C., Evaluation of Smoke Toxicity Using Concentration-Time Products, *J. Fire Sciences,* **2**, pp. 362-379, 1984.

[15] HUGGETT, C., The Forum: Reporting Combustion Product Toxicity Test Results, *J. Fire Sciences,* **3**, No. 2, pp. 79-82, 1985.

[16] LEVIN, B.C. *et al., Further Development of a Test Method for Assessment of the Acute Inhalation Toxicity of Combustion Products,* NBSIR 82-2532, National Bureau of Standards, Washington, D.C., 1982.

[17] PEACOCK, R.D. and BUKOWSKI, R.W., A Prototype Methodology for Fire Hazard Analysis, *Fire Technology,* **26**, pp. 15-40, 1990.

[18] *The Assessment of Toxic Hazards in Fire in Buildings and Transport,* BSI DD 180, British Standards Institute, Manchester, United Kingdom, 1989.

[19] LEVIN, B.C. *et al.,* Studies of the Toxicological Effects of Different Time Exposures to the Individual and Combined Fire Gases: Carbon Monoxide, Hydrogen Cyanide, Carbon Dioxide, and Reduced Oxygen, *Polyurethanes 88,* Proceedings of the SPI — 31st Annual Technical/Marketing Conference, Philadelphia, PA, October 18-21, 1988, Technomic Publishing Company, Inc., Lancaster, PA, pp. 249-252.

[20] PURSER, D.A., GRIMSHAW, P. and BERRILL, K.R., Intoxication by Cyanide in Fires: A Study in Monkeys using Polyacrylonitrile, *Arch. Environ. Health*, **39**, pp. 394-400, 1984.

[21] HARTZELL, G.E., GRAND, A.F. and SWITZER, W.G., Modeling of Toxicological Effects of Fire Gases: VI. Further Studies on the Toxicity of Smoke Containing Hydrogen Chloride, *J. Fire Sciences*, **5**, No. 6, pp. 368-391, 1987.

[22] KAPLAN, H.L. *et al.*, Respiratory Effects of Hydrogen Chloride in the Baboon, *The Toxicologist*, **6**, No. 1, p. 52, 1986.

[23] LEVIN, B.C. *et al.*, Toxicological Interactions Between Carbon Monoxide and Carbon Dioxide, Proceedings of 16th Conference of Toxicology, Air Force Medical Research Laboratory, Dayton, Ohio, October 1986; *Toxicology*, **47**, pp. 135-164, 1987.

[24] LEVIN, B.C. *et al., Synergistic Effects of Nitrogen Dioxide and Carbon Dioxide Following Acute Inhalation Exposure in Rats*, NISTIR 89-4105, National Institute of Standards and Technology, Gaithersburg, MD, 1989.

[25] PITT, B.R. *et al.*, Interaction of Carbon Monoxide and Cyanide on the Cerebral Circulation and Metabolism, *Arch. Environ. Health*, **34**, pp. 354-359, 1979.

[26] PURSER, D.A. and GRIMSHAW, P., The Incapacitation Effects of Exposure to the Thermal Decomposition Products of Polyurethane Foams, *Fire and Materials*, **8**, pp. 10-16.

[27] SAKURAI, T., Toxic Gas Tests with Several Pure and Mixed Gases Using Mice, *J. Fire Sciences*, **7**, No. 1, pp. 22-77, 1989.

[28] ESPOSITO, F.M. and ALARIE, Y., Inhalation Toxicity of Carbon Monoxide and Hydrogen Cyanide Gases Released During the Thermal Decomposition of Polymers, *J. Fire Sciences*, **6**, No. 3, pp. 195-242, 1988.

[29] HEIM, J.W., The Toxicity of Carbon Monoxide at High Altitudes, *J. Aviation Med.*, **10**, pp. 211-215, 1939.

[30] HARTZELL, G.E., GRAND, A.F. and SWITZER, W.G., Toxicity of Smoke Containing Hydrogen Chloride, *Fire and Polymers*, G. E. Nelson, Ed., American Chemical Society, Washington, D.C., pp. 12-20, 1990.

[31] BABRAUSKAS, V. *et al.*, Large-Scale Validation of Bench-Scale Fire Toxicity Tests, *J. Fire Sciences*, **9**, No. 2, pp. 125-148, 1991.

[32] LEVIN, B.C. *et al., Toxicological Effects of Different Time Exposures to the Fire Gases: Carbon Monoxide or Hydrogen Cyanide or to Carbon Monoxide Combined with Hydrogen Cyanide or Carbon Dioxide*, U.S.-Japan Panel on Fire Research and Safety, Center for Fire Research, National Institute of Standards and Technology, Gaithersburg, Maryland, May 1987.

[33] KIMMERLE, G., Aspects and Methodology for the Evaluation of Toxicological Parameters During Fire Exposure, *J. Fire and Flammability/Com. Tox. Supplement*, **1**, p. 42, 1974.

[34] PURSER, D.A. and BERRILL, K.R., Effects of Carbon Monoxide on Behavior in Monkeys in Relation to Human Fire Hazard, *Arch. Environ. Health*, **38**, pp. 308-315, 1983.

[35] HILADO, C.J., Relative Toxicity of Pyrolysis Products of Some Foams and Fabrics, *J. Comb. Toxicol.*, **3**, pp. 32-60, 1976.

[36] HARTZELL, G.E., GRAND, A.F. and SWITZER, W.G., Modeling of Toxicological Effects of Fire Gases: VII. Studies on Evaluation of Animal Models in Combustion Toxicology, *J. Fire Sciences*, **6**, No. 6, pp. 411-431, 1988.

[37] MATIJAK-SCHAPER, M. and ALARIE, Y., Toxicity of Carbon Monoxide, Hydrogen Cyanide and Low Oxygen, *J. Comb. Toxicol.*, **9**, pp. 21-61, 1982.

[38] HERPOL, C., MINNE, R. and VAN OUTRYVE, E., Biological Evaluation of the Toxicity of Gases Produced Under Fire Conditions by Synthetic Materials, Part 1: Methods and Preliminary Experiments Concerning the Reaction of Animals to Simple Mixtures of Air and Carbon Dioxide or Carbon Monoxide, *Comb. Sci. Technol.*, **12**, pp. 217-228, 1976.

[39] LYNCH, R.D., *On the Non-Existence of Synergism Between Inhaled Hydrogen Cyanide and Carbon Monoxide*, Fire Research Note No. 1035, Fire Research Station, Borehamwood, Hertfordshire, England, 1975.

[40] PURSER, D.A., GRIMSHAW, P. and BERRILL, K.R., The Role of Hydrogen Cyanide in the Acute Toxicity of the Pyrolysis Products of Polyacrylonitrile, *Arch. Environ. Health*, **39**, pp. 294-400, 1984.

[41] YAMAMOTO, K. and HUWAHARA, C., A Study on the Combined Action of CO and HCN in Terms of Concentration-Time Products, *Z. Rechtsmed.*, **86**, pp. 287-294, 1981.

[42] HARTZELL, G.E. *et al.*, Modeling of Toxicological Effects of Fire Gases: III. Quantification of