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FUELS AND FUEL ADDITIVES FOR HIGHWAY VEHICLES AND THEIR COMBUSTION PRODUCTS

A Guide to Evaluation of Their Potential Effects on Health

Committee on Toxicology

Assembly of Life Sciences
National Research Council

National Academy of Sciences
Washington, D.C.

1976

NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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I. INTRODUCTION

The Clean Air Act of 1970 increased the authority of the Environmental Protection Agency (EPA) to regulate fuels and fuel additives. Section 211 of the Act (PL-91-604) states that the Administrator

> "may require the manufacturer to conduct tests to determine potential public health effects of fuel or additives (including but not limited to carcinogenic, teratogenic or mutagenic effects)," and that "tests shall be conducted in conformity with the test procedures and protocols established by the Administrator."

Therefore, the need exists for selecting useful test procedures and protocols for predicting potential public health effects of fuels and fuel additives. These needs are further specified as "Proposed Rules" of the EPA.[19]

At the request of the EPA, the Committee on Toxicology of the National Research Council, assisted by the Advisory Center on Toxicology, proposed to evaluate the usefulness of existing protocols for predicting public health hazards that might be caused by environmental pollution from fuels, fuel additives and their combustion products arising from highway vehicles. The study was to be concerned with three principal areas:

> 1. the evaluation and recommendation of test protocols for necessary toxicologic investigations; 2. the collection of information on the composition of fuels, fuel additives and their combustion products; and 3. the development of a classification scheme for the substances involved, based on their known toxicity and potential as a public health hazard.

The present problem of setting emission standards for known toxic components, such as nitric oxide and nitrogen dioxide, sulfur dioxide, carbon monoxide and polycyclic aromatics, was not to be considered. However, evaluating changes caused by additives in the profile of combustion products was to be investigated. Suggestions were requested about mechanisms for systematically collecting and retrieving toxicologic data.

The Committee on Toxicology advised that a separate committee be formed to study the problem. The vice-chairman of the Committee on Toxicology served as chairman and one of its former members was appointed as a consultant. The new committee was named the Committee on Fuels, Fuel Additives and their Combustion Products. Liaison with EPA was provided by persons from the National Environmental Research Centers in Research Triangle Park, North Carolina and Cincinnati, Ohio, as well as headquarters staff.

Although the term "public health effects" could be interpreted to include many biologic effects, the Committee was asked to limit its consideration to protocols that might be useful in predicting effects on humans, and particularly to the evaluation of methods suitable for examining toxic effects of combustion products. However, it was recognized that toxicologic investigations of fuel additives per se would be essential nonetheless, because of the likelihood of direct contact with the fuel or its evaporative products. Protocols were desired for evaluating vehicular fuels, including all additives for fuel and lubricants, motor vehicle gasoline, and motor vehicle diesel fuel.

In February 1973, a working conference sponsored by the National Academy of Sciences at the request of EPA was held on Principles for Evaluating Chemicals in the Environment.[50] Several committee members, the consultant, and staff participated. Many concepts developed there directly relate to the current problem of designing effective protocols for evaluating the safety of fuels and fuel additives. Because the report has already been published, much of the material that evolved from the conference is not discussed in detail here. It is recommended that the reader consult that document. Wherever possible, the thinking developed in the conference report has been reflected in the conclusions of the committee.

Several documents were particularly valuable to the Committee in its search for information on the nature of fuels, fuel additives, and their combustion products; current views of the health effects of automotive air pollutants from fuels and fuel additives; and current suggestions for protocols for evaluation of materials in the environment.[20,21,42,50,51]

II. SUMMARY AND CONCLUSIONS

The Committee's principal concern was to evaluate protocols for experimental prediction of the hazards of automotive fuels, fuel additives, and their combustion products. The problem is so complex that it is questionable whether fixed protocols should be adopted now. Although techniques for inhalation toxicology are advancing rapidly, toxicologists have had little experience with automotive combustion products. Nor is there much information which would help to assess the predictive value of some methods now being developed.

The most clearly established human health responses from air pollutants are relatively simple and immediate, such as eye or possibly respiratory irritation and odors. Considerable evidence exists and these responses can be predicted by appropriate animal and human volunteer studies. Present data are too insufficient to establish whether fuel additives or their combustion products are carcinogens, teratogens or mutagens, and obviously data should be obtained. At present, procedures to evaluate such data are still in early stages and need much research. The interpretation of chronic toxicity data (including carcinogenesis) from animal inhalation, is not well standardized; it likewise needs evaluation, especially in regard to the significance of the studies to man.

Most fuel additives are organic, used in very low concentrations, and thought to be largely combustible. Exceptions include organometallics, organohalides, and sulfur compounds, which are partly combustible.

Finally, analytic methods for automotive combustion products have progressed to where their routine application in cases of changing fuels or fuel additives can provide a basis for tentatively predicting potential changes in hazards and for guiding the type of biologic research needed.

The Committee reached the following conclusions:

1. The initial evaluation of the safety of a new fuel-additive combination should include a comparison between a standard fuel and the new combination that considers the analytic profile of the combustion products and certain biologic effects.

2. The biologic methods suggested for the initial evaluation should be sensitive to the possibility that known health effects on humans from such sources may increase or diminish. They also should be able to detect unexpected toxic effects of fuels and fuel additives.

3. Separate considerations and more extensive research on most metal-containing additives should be required because of their persistence in the environment after combustion and their tendency to accumulate in the body.

4. All recommended methods will need careful validation and interlaboratory studies to determine their practicality and repeatability. They should be regarded as tentative and administrative flexibility will be needed if adopted for regulatory use.

5. Interpreting results of studies on combustion products is difficult at best, and decisions should be made by informed scientists who have considered all relevant information.

6. Appropriate epidemiologic and analytic studies should be conducted whenever new fuel-additive combinations are put into use, so that predictions made from experimental work may be confirmed or corrected.

III. CONSIDERATIONS IN DEVELOPING PROTOCOLS

As with other environmental problems, information on the chemical nature of the compounds to which people are exposed, routes of exposure, health of persons exposed, known or suspected effects of the compounds on human health, and evidence that experimental studies can predict such effects,[50] is necessary to develop protocols, such information is summarized below.

a. Composition of fuel additives and fuels

About 325 fuel additives were registered as early as 1972. They are usually added to the fuel in very small amounts (a few ppm to a few hundred ppm). They can be classified into about 15 chemical types (see Appendix III and reference 20). Fuels vary in their composition and physical properties, depending on use, seasonal and geographic factors, and origin (see Appendix IV and references 20, 21, 12, and 52a).

b. Sources of exposure to fuels, fuel additives, and their combustion products

As indicated in the diagram of Appendix I, the public is exposed to these materials in several ways. It shows four principal sources of exposure that may be hazardous to health: the risk of occupational hazards during the manufacture, blending and distribution of fuel additives; evaporative losses; the possibility that lubricants and additives contaminated by combustion products from piston blow-by may enter the environment as waste lubricants; and what the committee regards as most important, the inevitable human exposure to exhaust products before or after solar radiation.

Although fuel additives are largely nonvolatile, they are of course aerosolized during the mixing of the air and gasoline before combustion, and it is conceivable that traces might be carried out in uncombusted form, probably in the particulate fraction. The Committee is not primarily concerned with the effects of catalysts on automotive engine performance, but it does recognize that the catalyst or emission control systems may significantly alter the chemical nature of compounds found in the exhaust. It also recognizes that materials from the catalyst itself may escape into the exhaust stream. Some volatile components of fuel may be lost and they, along with some combustion products (NO_x, aldehydes) undergo photochemical reactions thought to account for some of the irritating properties in atmospheres which contain them. The organic portion of organometallic compounds is largely combusted and the metal is released in inorganic form.[45]

The many major classes of engines (gasoline, diesel, rotary, turbine, jet) use a large number of fuel additives and are operated in different modes. Each system produces different exhaust compositions and thus presents potentially different health and environmental hazards. Such diversity creates a problem in selecting and limiting the standard fuels, lubricants, and conditions of operations, for study in the type of engine for which new materials are being proposed. All these technical factors are crucial to the proper design of analytic and toxicological studies and will be discussed later.

c. Known and suspected health effects from combustion products

One of the most important principles in selecting protocols for the study of combustion products is to choose those that would predict most closely the best known acute or chronic human health effects. It is clear from both past and recent[42] reviews, that two acute effects of automotive air pollution are well established: the transient and reversible eye irritation observed with high levels of oxidants and odors from some types of exhaust. These effects probably arise from the fuel and its combustion products rather than from the small amounts of additive present.

The Committee suspects that other acute effects associated with automotive exhaust may include increased asthmatic attacks and deteriorating condition of people with pre-existing chronic bronchitis or heart disease. The anginal syndrome in persons with coronary disease may be aggravated by carbon monoxide exposure.[6, 7, 8] The exact cause of these suspected acute effects, or even their occurrence, is far from certain because of the difficulties of observation and the absence of reliable experimental animal models.

The most likely chronic effects of pollution by combustion products would be an increase in the amount or severity of chronic bronchitis and emphysema cases. Studies of increased respiratory disease in children and adults in areas with higher nitrogen oxide levels are poorly documented, and the need for more reliable epidemiologic studies is apparent.[42]

Polycyclic aromatic hydrocarbons isolated from auto exhaust have been found to be active in mouse skin carcinogenesis studies.[33,34,47,58,65] Lung cancer has increased more in cities than in rural areas, an elevation not entirely accounted for by smoking. However, definitive evidence that it is caused by auto exhaust is not available.[42]

Mutagenic compounds, including such materials as epoxides, have also been said to be part of air pollutants. However, no specific evidence relates chemical air pollution to human genetic mutation or teratogenesis. Although teratogenic effects are known to result from drugs, pesticides, hormones and viruses, they have generally occurred at relatively high dosage levels at critical stages or organogenesis. Thus, hazards to the fetus would arise primarily from exposure to high concentrations of pollutants during those critical stages.

d. Selection of practical approaches

Obviously the task of describing protocols which can evaluate public health effects from fuels and fuel additives and their combustion products is complex. These environmental contaminants comprise hundreds of different compounds, including virtually all physical and chemical forms of material (vapors, gases, aerosols, metals, and nonmetals). Moreover, the composition of the contaminants as breathed by humans will vary according to atmospheric conditions, photochemical reactions, engine characteristics, mode of engine operation and performance, effects of emission control devices, and interactions between these factors. Not only are original compositions variable, but it is increasingly clear that synergistic effects or altered responses from mixtures of various components may occur.[42]

Only a few environmental toxicologists have had experience in evaluating these compounds. The extensive records developed over the past 50 years on individual industrial chemicals, commercial products, and pharmaceuticals is lacking for environmental pollutants. Since the dosage levels from combustion products in the air is very much lower than those encountered with industrial chemicals, some consumer item and medications, it is inherently more difficult to detect and study the specific biologic consequences of fuel contaminants.

Although the Clear Air Act requires the Administrator to specify protocols and test methods, protocols based on our limited knowledge should be regarded as tentative. Their usefulness and practicality in predicting the safety of the combustion products of fuels and fuel additives should be continuously reviewed. The need for scientific judgement in the prescription of protocols also must be recognized, especially because of the uncertain validity of animal studies for predicting human health hazards from combustion products. Various types of exploratory research should be carried out and the most promising should be selected for continuation. The Committee reviewed the more important studies being carried out, and has recommended research priorities. They are set forth below.

e. The value of various methods for assessing biologic effects of fuels, fuel additives and their combustion products

Those procedures that are amenable to standard bioassay and statistical evaluation techniques that have long been used in other fields will have the greatest chance of success and therefore are assigned a high priority. Toxicologists have found that the simpler type of responses -- such as relative irritant potency, general toxicity potency, or reproducible physiologic or biochemical effects -- are most likely to elicit a successful dose-response curve which often can be clearly related to health effects known in humans. The best known and the first observed human responses (especially to air pollutants from automotive exhaust) are odor, eye irritation, and sometimes irritant effects on the upper and lower respiratory tract. These should constitute the first line of screening.

Although many studies have been carried out on air pollutants, few have been concerned with the sort of bioassay techniques of interest now. The most extensive series of long-term studies with whole exhausts is still underway.[38] Sponsored by EPA, it uses relatively sophisticated analytic methods and advanced techniques to generate atmospheres. This study would not be suitable for an initial evaluation, but it does provide valuable information from which better predictive tests may be eventually developed.

The role of in vitro test[20] in routine screening such as those suggested in the Durham Conference was considered by the Committee. These tests make use of condensates or particulate fractions from auto exhaust to which cells in tissue culture are exposed, or of isolated alveolar macrophages, etc. A variety of submammalian tests for mutagenesis, are also made. These tests may be very useful; however, they do need a thorough validation by direct comparison wherever possible with tests on intact animals.

It was suggested at the Durham Conference on Health Intelligence for Fuels and Fuel Additives[20] that if such in vitro tests were negative, the materials might be registered without further study; if they were positive, then it would be necessary to try various forms of in vivo study in animals and other experimental or epidemiologic studies. Because of the experimental nature and uncertainty of interpretation of such in vitro studies, the Committee felt it would be unwise to adopt this approach since if in vitro tests were negative, there would have to be some independent in vivo confirmation. If in vitro tests were positive, it would still be necessary to proceed with in vivo tests.

The Committee concluded that it would be better to use whole animal experiments and human volunteers (as recommended later in this report) wherever possible as the primary approach, and to plan for an orderly parallel evaluation of the various in vitro or other tests as a longer range program to develop quicker and less expensive screening tests.

Careful analytic study of condensates or fractions obtained by filtration is necessary to determine their constancy under standard conditions. Charleson reports that mass spectrometry has identified some 200 compounds from such sources.[42] It is also difficult to know whether information obtained by using condensates in experimental animals is comparable with that obtained with the same animals exposed normally to the generated atmospheres. Nevertheless, a thorough, systematic evaluation of the toxic properties of condensates might be valuable, at least in comparative studies between standard and new fuels. Evidently little work has been done on ordinary toxicology of condensates, that is, the determination of the LD_{50} (median lethal dose), evaluation of skin and eye irritancy, skin sensitization or other similar tests.

The Committee repeats its finding that the problem of evaluating the safety of fuels and their additives encompasses many difficult problems, and therefore the design of research programs should be extremely flexible.

f. Recommendations and comments

1. It is recommended that a standard test engine, as small as available, be selected. It should be operated in a minimum number of modes selected from the EPA standard engine cycling.

2. It is recommended that a comparison between a standard fuel-lubricant system with previously used additives and the same standard system using the proposed new additives be emphasized. The prime

objective of the initial evaluation should therefore be to develop reliable, appropriate comparative bioassays between standard and new fuel-lubricant systems.

3. It is recommended that protocols be chosen that might be expected to predict those human health effects that are most clearly known or suspected. For automotive air pollution, the most certainly established effects are eye irritation, odor, and respiratory irritation. Protocols for them are recommended below.

Other possible effects that are less clearly established -- chronic respiratory effects, carcinogenesis, teratogenesis and mutagenesis -- may need investigation. Research on protocols for predicting these effects is also discussed below.

4. It is recommended that analytic measurements of the exhaust profile constitute a major part of the investigation. The extent of such studies needs to be determined by experience. In some cases, these data might be crucial to judgements on safety and health. (But considerable advances in analytic techniques will be needed for maximal utility.)

5. It is recommended that the additive should be subjected to standard toxicological screening procedures described later even though primary concern is for the combustion products. This is because it is probable there will be direct contact with the product and it is conceivable that some amount of additive might escape combustion.

6. It is essential to know effects of a new fuel or fuel additive on the level of well known pollutants (carbon monoxide, nitrogen oxides, ozone, hydrocarbons) which are generated by irradiated or non-irradiated auto exhaust. The Committee did recommend the study of the biologic effects of such substances, since they already are the subject of past and present toxicologic and medical investigations.

7. It was recognized that novel problems and novel fuels (e.g., hydrogen, methane, methanol, etc.) might arise which would have to be considered eventually but have not been included in this report.

IV. ANALYTIC CHEMISTRY AND GENERATION OF EXHAUST EMISSIONS

Hundreds of compounds are present in the emission of fuel combustion, and it is practically impossible to detect and measure each one for the purposes of toxicologic experiments. However, by comparing the general profiles of exhaust components and specific classes of compounds from experimental fuels with those from standard fuels, it should be possible to make sound decisions on the likelihood of changes in health effects as well as the extent and type of toxicologic research needed.

a. Generation and irradiation of exhaust

The design of systems used for generating and controlling auto exhaust for toxicologic studies have been described by Hinners *et al*.[12,21,30] Since the raw exhaust is hot and contains lethal amounts of carbon monoxide, cooling and dilution are necessary before animals can be exposed. Procedures for exhaust irradiation are necessary and have been frequently described[12,21,53] because major increases in irritant effects have been noted after irradiation of exhaust. Although experimental atmospheres are reproducible some losses of particulates and condensation occur so that it is difficult to duplicate the conditions as they occur in outdoor atmospheres.

b. Purpose of analytic studies

Analytic studies are necessary for three purposes to: provide the necessary profile of exhaust products so new and standard fuels and fuel additives can be compared; monitor animal exposure, and help detect possible changes in biologic effects and the need for other toxicologic tests.

c. Analytic procedures

These procedures should include at least the analysis of carbon monoxide, total hydrocarbons, oxidants, nitrogen oxides. It also would be valuable to have information on the nature of exhaust hydrocarbons, olefins, and oxygenated compounds, polynuclear aromatics (PNA) content, particulates and metals. The analytic procedures used in EPA animal studies for characterization of exhaust systems have been described.[12,21] Necessary equipment includes carbon monoxide recorders, gas chromatographs, flame ionization spectroscopes, infrared and ultraviolet spectroscopes, filters and sizing equipment for particulates plus that required for various wet chemical methods.

Particle collection and analysis from auto exhaust is complicated--particles tend to be wet and sticky, making it difficult to determine their size and composition.[21,36]

Many analytic procedures that have already been worked out by industry and EPA to study exhaust composition as effected by changes in fuel and catalyst systems can be used in toxicologic procedures. For example, the standard federal test procedures include methods for recording carbon monoxide, exhaust manifold pressure, carbon dioxide, nitrogen oxide, oxygen, and total hydrocarbons. EPA regulations dealing with methods and other matters were published under Title 40 in the 25 November 1971 Federal Register.[16] Revisions appeared in Federal Register for 28 June 1973 [17] and 31 October 1973.[18] However, because human health effects as eye irritation may be related to the nature of hydrocarbons and oxygenated compounds, it may be necessary to use additional methods for studying these compounds such as those given by Wigg *et al*, Gross, and Heuss and Glasson. [27,29,62,63]

The fate of the fuel additive in the combustion process should be determined. To date, little work has been done on following radioactive labeled components of fuels and fuel additives to their fate in exhaust, probably because miniaturized systems for generating exhaust products necessary for practical use of radioactive tracers are unavailable. If such system were available the extent of combustion and the nature of products generated from additives in fuel-lubricant system would be more rapidly ascertainable.

The recent development of fuel injection systems may be an alternative to miniaturization. A fuel injection engine could be fitted with two switchable injectors. One could provide standard fuel, the other a fuel being tested. The resulting exhaust streams similarly could be switched between collection bags, analytic systems, or exposure chambers. The effect of the mode of engine operation on the exhaust would remain constant.

d. Some relations between analytic data and biologic effects

One of the major uses of analytic data will be to point to possible biologic effects that may need further study. At present, eye irritation is not thought to result from ozone *per se*, but to oxygenated compounds, or possibly nitro-olefins. Heuss and Glasson [29] studied the relation between hydrocarbon structures formed by exhaust irradiation and resulting human eye irritation. The benzylic hydrocarbons and aromatic olefins were felt to be potent precursors of eye irritation. Yeung and Phillips [66] also suggested that hydrocarbon structure and reactivity might be predictive. Alarie [1,2,3] has pointed out that lachrymators and similar compounds are often in a category of strong dienophiles. Perhaps the exhausts from fuels and fuel additives being tested should be examined for the occurrence and any major changes in such components. Polynuclear aromatics (polycyclic hydrocarbons) have been isolated from exhaust and skin painting on mice has shown them to be carcinogenic. Therefore, special attention should be paid to these fractions.

There has been increasing recognition of the importance of the interaction of air pollutants either in the atmosphere or even possibly within the lung itself. This phenomenon was discussed in a recent NAS conference, [42] where evidence was reported showing that the combination of ozone and sulfur dioxide would significantly increase the acute pulmonary irritant effects in humans. The possibility of any increased formation of sulfur compounds to acid sulfates in fuel and fuel additives should be investigated.

V. RECOMMENDED APPROACHES FOR EVALUATING FUELS AND FUEL ADDITIVES

Based on previous discussions and the assumption that organic components will be largely combusted, it is recommended that all new fuels and fuel additives be evaluated initially in comparison with the standard as follows:

1. Obtain acute toxicity data on the oral LD_{50}, skin and eye irritation, skin sensitization, and an inhalation LC_{50}, (median lethal concentration) on the compounds before combustion and compare them with standard materials.
2. Determine the acute and short-term LC_{50} or LT_{50} (median lethal time) by inhalation of the diluted exhaust, both before and after irradiation and compare them with exhaust from standard fuel and clean air as a control.
3. Determine eye irritation of exhaust before and after irradiation and compare with standard fuel and with clean air as a control.
4. Evaluate the acute irritant effects of exhaust on the respiratory system before and after irradiation and compare with standard fuel and with clean air as a control.
5. Evaluate the odor potency and olfactory characteristics of exhaust and compare with standard fuel exhaust.
6. Evaluate the exhaust analytic profile before and after irradiation and compare with exhaust profiles of standard fuel.

The above methods should provide an initial evaluation of effects on the eyes and respiratory tract as well as on the target organs most clearly involved in the known human health effects of pollutants from automotive exhaust.

Few problems should be encountered in developing acute toxicity information such as the oral LD_{50} and skin and eye irritation with fuel additives *per se* since standard methods should suffice. For acute inhalation of fuel additives, some difficulties may be encountered if they are not volatile. Aerosol techniques would be needed and it may be difficult to aerosolize such materials.

Any proposed animal studies of eye irritation would require validation with human experience. Not only has there been little correlation between animal and human work, but the most pertinent information about eye irritation caused by air pollution has come from human subjects. Hamming and MacPhee [28] evaluated the role of NO_x in eye irritation. Panels of five members were exposed through eye ports and a quantitative study was made from the time of exposure to the first onset of irritation. The work of Heuss and Glasson [29] has been mentioned.

Using 16 chemicals and irradiated auto exhaust, Buchbert *et al* [11] evaluated the interaction of several atmospheric variables. Wilson and Levy [64] were concerned with the role of sulfur dioxide in photochemical aerosols in eye irritation from photochemical smog. Seven-member panels were used and a determination made of the time of exposure to onset of irritation. The above studies can be used as guides to the equipment and procedures needed for development of a standard method for measuring human eye irritation. Research is recommended for developing such methods and correlating them with parallel animal studies. Determination of odor requires human subjects, and a considerable amount of basic information is available on the measurement of odor potency. Leonardos et al used an environment low in odor and evaporated measured liquid volumes of pure chemical.[37] Four experienced panel members were used for each test. Only one test was performed per day on any subject. Such methods are useful for determining the minimum identifiable odor under ideal circumstances. Rounds and Pearsall correlated diesel exhaust gas odor with exhaust gas composition.[54] Fiala and Zerchmann[23] used a dilution technique to determine the minimum identifiable odor. It seems feasible to carry out odor studies in conjunction with eye irritation experiments using the same generating equipment.

The Committee recognizes the difficulties in recommending the use of human subjects for any type of toxicologic investigation.[14,49] However, little hazard is involved in this sort of study, because the exposures are to relatively dilute materials for a few seconds or a few minutes. Despite the innocuous nature of such studies, all customary procedures and explanations to volunteers should be explained. These studies should be under medical supervision and preceded by appropriate animal experiments. It is possible that unusual irritant effects or odors may be noted during the study of the effectiveness of new additives or fuels. Any such events should be fully documented and noted. Attempts should be made to document the presence or absence of adverse effects in the synthesis, handling, or testing of any new fuels or additives.

Additional approaches needed for organometallics are discussed in the following section.

VI. AN OUTLINE OF PROPOSED EXPERIMENTAL ANIMAL PROCEDURES FOR EVALUATING THE SAFETY OF FUELS AND FUEL ADDITIVES USED IN INTERNAL COMBUSTION ENGINES.

The procedures are suggested for the initial evaluation of a new fuel or a fuel additive. They are tentative and some have not previously been applied for this purpose. The principal objectives are to detect qualitative or quantitative differences between standard and new fuel-additive systems before and after combustion and provide additional assurance that unexpectedly toxic or irritating substances are not present in effluents. Because of the tentative nature of the protocols, the experimental design and selection of species should be extremely flexible. Similarly, scientific judgment is needed to interpret the data. As experience is obtained, more precise methodology may be prescribed for regulatory purposes. In the absence of such experience, the suggested procedures are grouped according to their potential for quick inexpensive reproducible results which can most reasonably be translated to man. From these EPA should select those procedures for their applicability to the nature of the product, volume of use, extent of distribution, and associated degree of public exposure. It should be noted that none of the recommended procedures are without cost and for some the costs may be significant. All data should be evaluated using appropriate statistical methods.

a. Methods for evaluating the toxicity of fuels and fuel additives before combustion

Group 1 - High Priority:

- Determine the oral LD_{50} in 2 species preferably the rat and mouse by following the procedures of the Federal Hazardous Substances Act and NRC Publication 1138.[44]

Problems may be encountered in finding suitable solvents or suspending agents for such compounds and the toxicity of such solvents or vehicles should be determined at the same time. Observe the animal for weight gain, food intake, and signs of toxicity for 14 days after administering the dose.

- Determine primary irritation and acute dermal toxicity with rabbit skin in the manner described in the Federal Hazardous Substances Act.[44]

For primary irritation and acute dermal toxicity, it would be useful to have the additive dissolved in the same solvent used for its incorporation into fuel. Modifications in this technique will be needed if such solvents cause too severe an irritation under an impervious cuff.

- Determine the eye irritation capacity in the rabbit eye using the procedures in the Federal Hazardous Substances Act.[15,44]

Although the validity of applying results from rabbit eye to predict human eye irritation has been questioned, this method probably is useful for comparative purposes. It will be preferable if and when it is correlated with human studies. Since the fuels and some fuel additives are volatile compounds, it is desirable to have a suitable method for determining acute eye irritation from exposure to vapors. Perhaps a procedure similar to Keplinger's [32] could be adopted for this purpose. Since the procedure has not been published, it is presented in Appendix II. It will, of course, need validation.

- Determine the acute inhalation toxicity in two species, preferably rat and guinea pig, by the inhalation procedures described in the NRC Publication 1138.[44]

Group 2 - Intermediate Priority:

- Determine skin sensitization using the guinea pig in a manner similar to that described in NRC Publication 1138.[44]

Although strong skin sensitizers in the guinea pig are frequently strong skin sensitizers in man, a negative result in the guinea pig does not necessarily mean that the compound will be inactive in man. Human patch tests are frequently used to confirm negative data in guinea pigs.

Based on the above animal data and any available information on irritant or toxic effects in workers handling such compounds, fuels and fuel additives could be classified as to skin or eye irritancy and systemic toxicity by any route of administration, according to the scheme used in NAS-NRC Publication 1465, January 1974 Revision.[43] Some modifications may be needed to adapt the scheme to fuels and fuel additives. This rating system is outlined in Appendix V. The rating system of Hodge and Sterner [31] may also be useful.

b. Methods for evaluating the safety of combustion products of fuels and fuel additives

The principal objective is to determine the qualitative or quantitative differences between the standard fuel and new fuel or fuel additive. Such studies are considerably more complex than those dealing with additives *per se*, because of the elaborate equipment and controls needed for generation and analysis of the combustion products. Interpretation of results may not always be precise.

The test vehicle and chassis dynamometer should be operated according to federal test procedures. Provision should be made for control air purification and for cooling and dilution of the exhaust. Appropriate size and type of exposure chambers will be needed. (See also Section IV). Hinners *et al*. [12,21,30] have described methods used for producing and irradiating automobile exhaust in connection with the EPA animal studies.

Group 1 - High Priority:

- Pulmonary irritation

Evaluate the acute respiratory irritant effects in guinea pigs using techniques of Murphy and Ulrich,[41] or Amdur and Mead,[5] or in mice by the method of Alarie.[1,2,3]

The purpose of these studies is to determine the irritant effects on either the upper or the lower respiratory tract by measuring respiratory flow rates, respiratory frequency, tidal volume, and compliance. The principles used are those developed by Amdur and Mead.[5] Murphy and Ulrich[41] modified their technique to permit the use of several animals at a time although at the expense of losing the compliance data. They also eliminated the need for inserting intrapleural catheters, and the animals can be exposed repeatedly as well. Experience may show that measurement of respiratory functions in other species will be equally useful.

Exposures should be about 4-6 hours to at least three concentrations. In general, irritants tending to affect the upper respiratory tract will cause flow resistance to increase and frequency of respiration to decrease. Irritants such as ozone and nitrogen dioxide which affect the lower respiratory tracts, may not affect flow resistance much, but they will cause a delayed increase in frequency of respiration. Direct measurements show compliance[5] decreases with irritants affecting the lower respiratory tract. In the guinea pig exposure periods of at least an hour appear to be needed to reach a plateau for upper respiratory irritants, and 3-4 hrs for lower tract responses. The percent change in response from control is plotted against concentration of oxidants, nitrogen dioxide, or total aldehydes to determine the 50% change from control values.

Alarie[1,2,3] has described methods for evaluating sensory irritant effects on the respiratory tract by measuring respiratory frequency in mice exposed for 3 min. to relatively concentrated vapors of pure substances. His procedure has not been applied to whole automotive exhaust products, but it may be a relatively simple method of detecting upper or lower respiratory tract irritants in automotive exhaust. The short duration of exposure would allow relatively high concentrations of exhaust to be used without encountering significant toxic effects from carbon monoxide. Concentration is plotted against percent change in response relative to control values. Both these methods should be validated by interlaboratory studies using the most identical exposure conditions possible. The following three other published procedures may be helpful in evaluating acute pulmonary effects if results from previously described studies are conflicting or doubtful. They provide different indicators of pulmonary responses:

i. One of the characteristic effects of irritants affecting the lower respiratory tract is protein leakage into the alveolar spaces. This effect has been studied by measuring the wet weight of the lung, and by recovering iodinated albumen from the alveolar spaces 6 hr after its intravenous injection into exposed rats. Such techniques could be applied to rats exposed to exhaust before and after irradiation. Alpert et al.[4] applied this method to ozone. Six-hr exposures to ozone at levels as low as 0.5 ppm showed significantly increased quantities of radioactivity in the lavage fluid. Lung wet weight measurements were somewhat less sensitive, showing effects at 2.5 ppm ozone. Lung lavage and dis-gel electrophoresis have also been used to study effects of nitrogen dioxide.[59]

ii. Lately, attention has been paid to the role of alveolar macrophages in removing particles and some infectious agents (such as bacteria) from the respiratory tract.[9,10] Effects appear relatively rapidly and are capable of some quantitation. Injections of the living bacterial organisms such as staphylococcus aureus permit the functional activity of macrophages to be evaluated; by sacrificing the animals after a short time for phagocytosis of organisms, homogenization of the excised lung, and counting the viable and nonviable organisms recovered from the homogenate.[26] Brain[9,10] has also given details of techniques for measuring the number of alveolar macrophages and certain functional parameters after intratracheal injection of particles.

iii. The technique of evaluating the clearance mechanisms of the lungs by inhalation of inert particles such as titanium dioxide (TiO_2) after exposure to irritants has recently been explored in many laboratories. In this type of experiment, rats are exposed to varying concentrations of irritant gases for approximately 7 hr/day, 5 day/wk for about 70-170 hr. At the end of that period, the animals are exposed for 7 hr to a respirable size titanium oxide aerosol at a concentration of 15 $\mu g/m^3$. Comparable doses of titanium oxide are given to controls and the total lung content of retained titanium oxide in individual rats determined chemically. One-hundred seventy hours exposure to sulfur dioxide at as low as 1 ppm was concluded to have caused a depression of the rate of lung clearance of titanium oxide.[22]

- Eye irritation

Keplinger's technique[32] as described in Appendix II uses a relatively short exposure of 60 seconds. It is probable that a longer exposure would be needed for diluted auto exhaust. Irradiated exhaust should be the focus of research because human data indicate that it is the primary source of human eye irritation. The effect of condensates from irradiated auto exhaust applied directly to the rabbit eye and scored by the Draize method[15] has not been studied much. Freeze-out or filtrate samples applied to the rabbit eye at intervals after irradiation might provide an index of irritancy.

Hamming and McPhee[28] have provided basic information on sensory effects of pollutants on the human eye. The exposures were extremely short--less than 4 min--and the sensory irritant effect was rapidly reversible. Eye ports in the irradiation chambers were provided for panels of five members and the time to onset of sensory irritation was noted. The geometric mean of the number of seconds to initial detection of the irritation was calculated for members of the panel. Animal studies need to be correlated with human data to make future extrapolations and predictions more meaningful.

- Odor determination

Brief exploratory experiments have been done to date, mostly with diesel exhaust. The techniques for odor threshold determination of chemicals used by Leonardos et al.[37] should be applicable to auto exhaust. The exposure time for recognizing odor at varying concentrations of exhaust would be very short. Sampling ports and air dilution facilities would be needed. It is best to use trained subjects who have demonstrated an ability to distinguish odors critically.

Group 2 - Intermediate Priority.

- Using irradiated and non-irradiated exhaust with at least 3 dilutions each, determine an approximate LC_{50} for a 4-6 hr exposure with groups of 10 male rats and 10 male guinea pigs for each exposure. Determining an LT_{50} may also be useful.[21]

Observation should include analysis of blood carboxyhemoglobin at the end of the exposure, observations of survivors for 14 days, and measurement of weight loss or gain, behavior and food intake. The purposes of the study would be to discover any acute toxic effects other than those expected from carbon monoxide, to provide a background for other studies on pulmonary effects, and determine needed dilution levels for such experiments. For example, it is known that guinea pigs can tolerate about 500 ppm carbon monoxide for 4 hr with little or no effect on their respiratory function.[40] More inhalation bioassays are needed to determine optimal conditions and species.

Perform repeated 4-6 hr studies with rats and guinea pigs at the maximum tolerated concentration noted in single dose studies and at one-fifth of the maximum tolerated concentration in exposures repeated daily, 5 day/wk for at least 2 wk. Autopsies should include measurement of blood carboxyhemoglobin; weights of lung, liver, and kidneys histologic examination of selected tissues. Depending on the nature of the fuels or fuel additives and of analytic data on exhaust products, longer and more complex pathologic studies may be required of other organ systems (hematologic, central nervous system, renal). Various biochemical indicators of response and tissue analyses may prove useful.

c. Evaluating hazards of metal-containing additives

Group 3 - Low Priority:

No specific methods are suggested because extensive research and long-term studies are necessary to evaluate hazards. Determining the chemical form of the metal in the exhaust, and its particle size and other characteristics will be important for predicting the hazard. Special attention should be given to the presence of metal carbonyl compounds. Recent NAS publications on lead[45] and manganese[46] review pertinent literature. Metals tend to persist in the environment after combustion and may enter the food chain.[24] They also may enter the body by inhalation and some are skin sensitizers. Some may interact with essential trace metals. A number of metals also tend to persist in the body; therefore, acquiring data on their absorption, excretion and biological half-times is important.

The report of the task group on metal accumulation of the Permanent Commission and International Association on Occupational Health [52] provides a comprehensive discussion on evaluating this aspect of metal toxicity. The 1972 annual report of EPA's Environmental Toxicology Research Laboratory [21] gives several examples of preliminary screening examinations for evaluating metal toxicity.

Much information is already available on many metals that could be used in preliminary evaluations. For some metals (such as lead), it is possible to find the critical organ concentration, and make extrapolations from it on the likelihood of health hazards from environmental contamination. [52] Many metals can be neutron-activated to facilitate study of their metabolic fate, but their use in combustion product toxicology will be limited unless the combustion process can be greatly miniaturized. However, modern analytic techniques can determine many metals with sufficient precision and specificity without tagging.

d. Carcinogenesis, mutagenesis and teratogenesis

Group 3 - Low Priority:

As mentioned, evidence for the occurance of these effects in humans in relation to air pollution is considerably more uncertain than those related to primary irritation. Attempts to induce lung cancer in animals by direct inhalation of air pollutants have generally been unsuccessful and experimenters have resorted to direct implantation techniques or intratracheal injections as well as the use of adjuvants such as iron oxide or carbon particles. [55] Only a few chemical agents, e.g., bis-chloromethyl ether and vinyl chloride, have shown pulmonary and systemic carcinogenic effects when inhaled. [35,39,57,61] Skin painting techniques in mice using particulate fractions from auto or aircraft engine exhausts have shown carcinogenic activity. [33,34,47,58,65] From the literature, it is expected that skin painting with appropriate particulate fractions would be the most probable choice for a useful comparative bioassay. Intratracheal techniques may also prove useful, but measuring quantitative or relative potency of carcinogens is much more difficult than that of systemic toxicity or relative irritancy. It is unknown whether any techniques lend themselves to a reliable extrapolation to human carcinogenesis of combustion or exhaust products as naturally encountered. If carcinogenicity tests are conducted the data should be considered as research information rather than being used for regulatory purposes without confirmation.

Useful guides have been written to the study of mutagenesis, teratogenesis, and carcinogenesis. [13,50,60] Some variation of the dominant lethal test exposing male rats or mice to inhalation at several dose levels might offer promise of a useful bioassay, but considerable validation would be necessary before specific recommendations could be made. Pregnant rats have been exposed to varying doses by inhalation at appropriate times to elicit potential teratogenic effects, but no recommendations can be made on the usefulness of this approach for automotive exhaust. High concentrations of certain solvents have been shown to have potential toxic effects on both embryo and fetus.[56]

e. Behavior studies

Group 3 - Low Priority:

No recommendations are made at this time because the usefulness of such studies as comparative bioassays for auto exhaust has not been determined. However, EPA exploratory research [21,25] appears to indicate that simple wheel running activity in rats is depressed considerably during exposure to auto exhaust; it is apparently not caused by carbon monoxide although other gaseous components or irritants may be involved. The depression disappears upon cessation of exposure. Water licking of rats was also depressed, but it was complicated by a simultaneous weight loss. Studies of spontaneous motor activity might lead to development of a comparative bioassay for acute effects, although the mechanism may be a nonspecific, protective response to exposure to irritant gases or other components. Again, complex animal behaviors need to be correlated to human activities. It is suggested that EPA monitor the progress of this developing field for additional methods.

f. Summary comment

Tests suggested for use with the fuels, additives, or their combustion products in the Group 1 High Priority category should be considered minimum tests to be applied to all candidate materials. Those in the Group 2 Intermediate category may provide data to supplement the findings of Group 1 procedures.

Those tests in the Group 3 Low Priority category are generally expensive--about $50,000 to $100,000--and their application to man is controversial. In addition, the sensitivity and reproducibility of these procedures is in question. In view of these factors and the low levels of exposures of the public this group of procedures will probably be of use only for materials in high volume use with wide distribution, resulting in widespread exposures.

VII. CRITERIA FOR EVALUATING HEALTH HAZARDS

The following recommendations for evaluating human health hazards from the proposed analytic and toxicologic studies should be regarded as tentative until sufficient experience is acquired in the use of new procedures.

Before commencing any analytic or toxicologic studies, a thorough search should be made of the published literature and available unpublished reports. Some compounds may be rejected at once for toxicologic reasons, e.g., highly toxic metals such as mercury, thallium, etc. A special effort should be made to document any observations on occupational hazards in the course of synthesis or handling of compounds. It is also assumed that comparative data will be available on the extent of use, and that methods for determining appropriate compounds will be available in the gaseous and particulate phase of the exhaust.

The proposed scheme for evaluating health hazards from the combustion products of a new fuel-lubricant system consists of a combined comparison of the analytic and toxicologic profiles of an appropriate standard system with those of a candidate new system. The simpler toxicologic studies can proceed independently of the analytic determinations; however, an evaluation of the nature and amount of some selected exhaust components will usually precede the more complex toxicologic studies. Some analytic methods will be required for monitoring exposures of animals. Important considerations in evaluating health hazards follow.

a. Analytic data

1. The most important comparisons will be those of the type and amount of selected components between standard and test materials and before and after irradiation. It is possible for a given component to make up a relatively larger proportion of the pre-irradiated exhaust and ultimately to become lower in concentration, depending on precursors or rates of reaction, for examples, a change in profile with a shift toward oxygenated materials, aromatic olefins or benzylic hydrocarbons might indicate the possibility of new types of primary irritants. Primary irritant responses often have steep dose-response curves; therefore, precise determinations of concentrations encountered by the exposed animals are important.

2. Changes in the typical temporal course of the appearance and die-away curves of major oxidant components such as nitrogen dioxide and ozone might reveal changes in probable biologic effects, which in turn would suggest appropriate biologic studies.

3. Increases in total concentrations of nitrogen dioxide, oxidants, nitro-olefins or nitrated peroxy compounds, dienophils or other structures typical of lachrymators or pulmonary irritants are undesirable and would require primary irritation studies.

4. Increases in polycyclic aromatic fractions or changes in their type might lead to consideration of comparative carcinogenic tests such as skin painting in mice.

5. For stable organic additives or those having relatively imcomplete combustion more thorough and long-term studies on the inhalation toxicology of the additive *per se*, would be indicated. It is desirable to know the chemical fate of an additive--whether it was present in the exhaust in gaseous or vapor form, particulate phase, or ash. Knowing the size and physicochemical behavior of particles would be helpful when considering the probability of particles being retained in the lung. This knowledge will help identify the toxicity test procedures and observations.

6. In the case of organometallic compounds, determinating the amounts present in the exhaust and their persistence in the atmosphere are essential, as many organometallics have different toxicity than the metal or its inorganic compounds.[45]

7. Present knowledge is inadequate for evaluating the hazard of a component in fuels, fuel additives, or their combustion products based upon its class of organic compound. Toxicity varies widely within classes.

b. Toxicologic data

1. Data from studies of additives or novel fuels *per se* should allow judgments as to the type and potency of acute toxic effects when compared to standard materials. Judgments should not be difficult, because the techniques used are well known and permit classification. More extensive studies may be needed if no combustion occurs. Observation of new types of toxic effects not seen with standard materials or the detection of significantly delayed responses might also require additional work. The data will be particularly useful for evaluating occupational hazards and making some initial judgments of public hazards if the substance is found unchanged in the exhaust. The estimation of hazard demands a knowledge of exposure levels as well as the type of response and potency of the compound.

2. Interpreting post-combustion toxicity data requires especially careful comparison with data on standard systems and with analytic data. If procedures must be chosen, post-irradiation data are probably more significant, based on the literature. Certainly any definite increases in eye irritation, especially if confirmed in humans, would be an adverse finding. Such tests are conducted under exaggerated conditions, and might, if other factors warranted, be repeated under less severe or more normal circumstances. The same would apply to odor potency or unpleasantness.

Clearcut evidence of comparatively increased primary irritant effects on the upper or lower respiratory tract in pulmonary ventilation studies would imply that clearance studies and explorations of effects on phagocytosis[26] be undertaken.

Alveolar protein leakage could be evaluated if evidence were obtained of lower respiratory irritation or increases in lung weight. Consistent reporting of increased pulmonary tract irritation at lower than standard concentrations would suggest an increased hazard.

3. Metals present particularly difficult problems in interpretation. The critical organ concentration concept provides a useful approach in some cases, but it requires extensive and usually unavailable metabolic and toxicologic data. Possible interference of metal contaminants with essential trace metals should be considered, the environmental pathways of metals, which may be sources of food and water for humans and animals, must also be considered.

4. Interpreting carcinogenic studies is also difficult; more data are needed to show that dose-response curves can be reliably repeated for comparisons. Further experimental and epidemiologic research on carcinogenesis and mutagenesis is needed. Analytic evidence of exhaust components closely related chemically to known carcinogens would require comprehensive toxicologic evaluation.

5. Classification of effects

Since the approach suggested is to compare new and standard conditions, a simple classification of increase, decrease or no effect in analytic and toxicologic parameters would be useful in an initial scrutiny of data. A further grading of slight, moderate or marked increases or decreases could be made if warranted by studies on the reliability and reproducibility of data. For instance, an oversimplified evaluation is explained below.

Analytic Data		Toxicity of Exhaust		
CO		Eye irritation)		
HC		Odor)		Indication of
NO_x	plus	Pulmonary irritation)	equals	Relative Hazard
O_3		Inhalation toxicity)		
Oxidants				
Polynuclear Aromatics				
Aldehydes				
Metals				
Particulates				

The test material would be rejected or studied further if either its analytic or toxicity data showed significant increases beyond those of the standard. If these data were the same or less than the standard the material would be accepted.

As declared,[50] it will be necessary to consider all available information, as no routine hierarchy of test procedures is completely reliable. There is no substitute for the informed judgment of scientists at present.

VIII. DATA COLLECTION, STORAGE, AND RETRIEVAL SYSTEMS

It is important that EPA have an available system for collecting, storing and retrieving data on the safety of fuels, fuel additives, and their combustion products. The system need not be automated, because the total number of materials involved is not large. Such a system should be capable of rapid up-dating, easy expansion (preferably open-ended), and should include multiple indexing and cross-indexing to permit several entries. Besides the mechanics of automatic or manual data processing, professional capability for organizing the data and performing preliminary evaluations and interpretations is necessary.

The nucleus of this kind of system may exist in several places. A comprehensive study has not been made, but among those known to the Committee, the most promising organizations are:

Advisory Center on Toxicology
National Academy of Sciences
2101 Constitution Avenue
Washington, D.C. 20418

Air Pollution Technical Information Center
Environmental Protection Agency
Research Triangle Park, N.C. 27711

BioSciences Information Services
2100 Arch Street
Philadelphia, Pa. 19103

Technical Information Services Branch
National Institute of Occupational Safety and Health
P. O. Building
5th and Walnut
Cincinnati, Ohio 45202

Specialized Information Services
National Library of Medicine
8600 Rockville Pike
Bethesda, Md. 20014

Toxicology Information Response Center
Oak Ridge National Laboratory
P. O. Box Y
Oak Ridge, Tenn. 37830

IX. RECOMMENDATIONS FOR RESEARCH

Throughout this report, the Committee has repeatedly pointed out the need for further research, especially in the area of combustion product toxicology. It should not be difficult to evaluate fuel additives or new types of fuel *per se* before combustion, since traditional toxicologic procedures can be adapted to these needs easily.

Present difficulties in the conduct of toxicologic studies on combustion products lie not only in the massive outlays for equipment and personnel needed to plan, analyze and control the facilities for proper generation and irradiation of combusted products, but also in the lack of clearcut knowledge about human responses to air pollutants in relation to any specific categories of substances. Now it appears that adverse health effects may arise not only from single isolated pollutants, but from mixtures and complex chemical reaction products and from physicochemical and biologic interactions among the pollutants. (See Appendix VI) The greatest research needs are listed below.

a. Analytic methods

Despite extensive research and much available knowledge, we are still not able to determine the material or class of materials responsible for eye irritation, one of the major symptoms related to automotive exhaust. Research needs to be continued to detect and measure materials in the class of known lachrymators and test them individually to see whether they are actually responsible or if their effects are additive. Little is known now about the fate of the organic fuel additive molecules, although it is presumed that most are more or less completely combusted. Research needs to be continued on the generation and fate of complex reaction products, which should be studied not only in smog chambers, but in actual atmospheric situations.

b. Miniaturization of the combustion process

The Committee believes that miniature engines or combustion processes to facilitate toxicologic research should be developed. At present, the massive equipment such as V8 automotive engines are satisfactory for functional and technical studies. However, they are awkward and impractical for general toxicologic investigation of such materials as the toxicology of combusted fuel additives, especially in the early phases of screening new additives for potential toxicity, when ideally only relatively small exposure chambers are used. It is possible that engines burning fuel on a steady state rather than in a batch process could be used, but such equipment would need to be tested thoroughly to determine the analytic profile of the exhaust products.

Miniaturization would also make it possible to use radioactive tracers or stable isotopes to study the fate of fuel additives, metals, and components of new fuels. Irradiation of exhaust products would be much simpler with smaller equipment. Perhaps the serious losses of material that now occur when automotive engine exhaust is conducted through the irradiation chamber to the animal exposure chambers could be minimized. It might be worthwhile to try a fuel injection engine modified for switching from a standard to a test fuel and which could separate exhausts.

c. Eye irritation

Useful experiments with eye irritation in animals exposed to whole exhaust are limited, because most species simply close their eyes and nictitating membranes to avoid contact with the suspected irritant. Proposed techniques for studying fuels and fuel additives have not yet been validated, and it seems unlikely that we will know whether such techniques are useful for predicting human eye irritation unless human volunteers are observed. Although there are problems in the use of human volunteers, the hazard in this case is minimal because of the very short exposure times needed and because past experience with human volunteers has shown that very successful research can be carried out with eye ports in standard smog chambers. Similar reasoning applies to the determination of odor, which can only be measured with human subjects.[48]

d. Use of condensates and filtrates

These substances are potentially useful because experimental conditions can be very much simpler than those in which animals are exposed to full exhaust. However, with the exception of painting mouse skin for carcinogenesis studies, few measurements and bioassays of the irritant or other toxic effects of condensates on the eye, the skin, and by intratracheal injection have been reported. Little data appear to be available on the toxicity of such condensates, and systematic exploration might be useful for purposes of comparative bioassay although direct extrapolation to human health might be difficult or impossible. Methods for collecting condensates would have to be carefully studied and the difficulties in reproducing condensates would have to be minimized by attention to procedures and proper analytic studies, including interlaboratory collaborative tests. The relation between data from condensates and data from actual exposure to emissions would have to be established.

e. Interactions of irradiated exhaust effluent compounds with sulfur dioxide or other materials

The interactions between ozone and sulfur dioxide may greatly increase the toxic effect, probably because sulfuric acid and acid sulfate aerosols are formed. After irradiation, it is conceivable that a fuel additive or a new fuel might produce a different type of oxidant mix in the atmosphere. Therefore, such interactions should be explored whenever major changes are made in fuels or fuel additives. The existence of interactions could be ascertained by analytic methods and pulmonary function tests.

f. Epidemiology

Epidemiology is not of particular interest to this report, but epidemiologic studies should be continued and improved.[42] Some suspected adverse effects attributed to one or another of the chemical air pollutants may have been caused not only by primary pollutants themselves, but with other as yet unknown and unidentified reaction products generated in the atmosphere or within the lung itself. If major changes are made in fuel additives or types of fuel, it would be desirable (although obviously difficult) to prepare for epidemiologic studies carried out over long periods of time and in diverse communities to determine whether trend exists in the occurrence of disease that might be related to such sources.

g. Validation

Several suggested procedures have not been subjected to scientific peer review. Others have not been replicated in other laboratories. It is important that any procedure adopted for screening purposes or regulatory action should be thoroughly validated for its sensitivity, reproducibility and, if possible, its correlation with human effects.

h. Occupational exposures

Manufactures of fuels, lubricants, and additives should be encouraged to collect data on levels of occupational exposures to such products and the associated effects (if any). Such data should be made available for use in evaluating the environmental effects of a product. EPA should explore ways of obtaining these pertinent occupational exposure data from NIOSH and OSHA.

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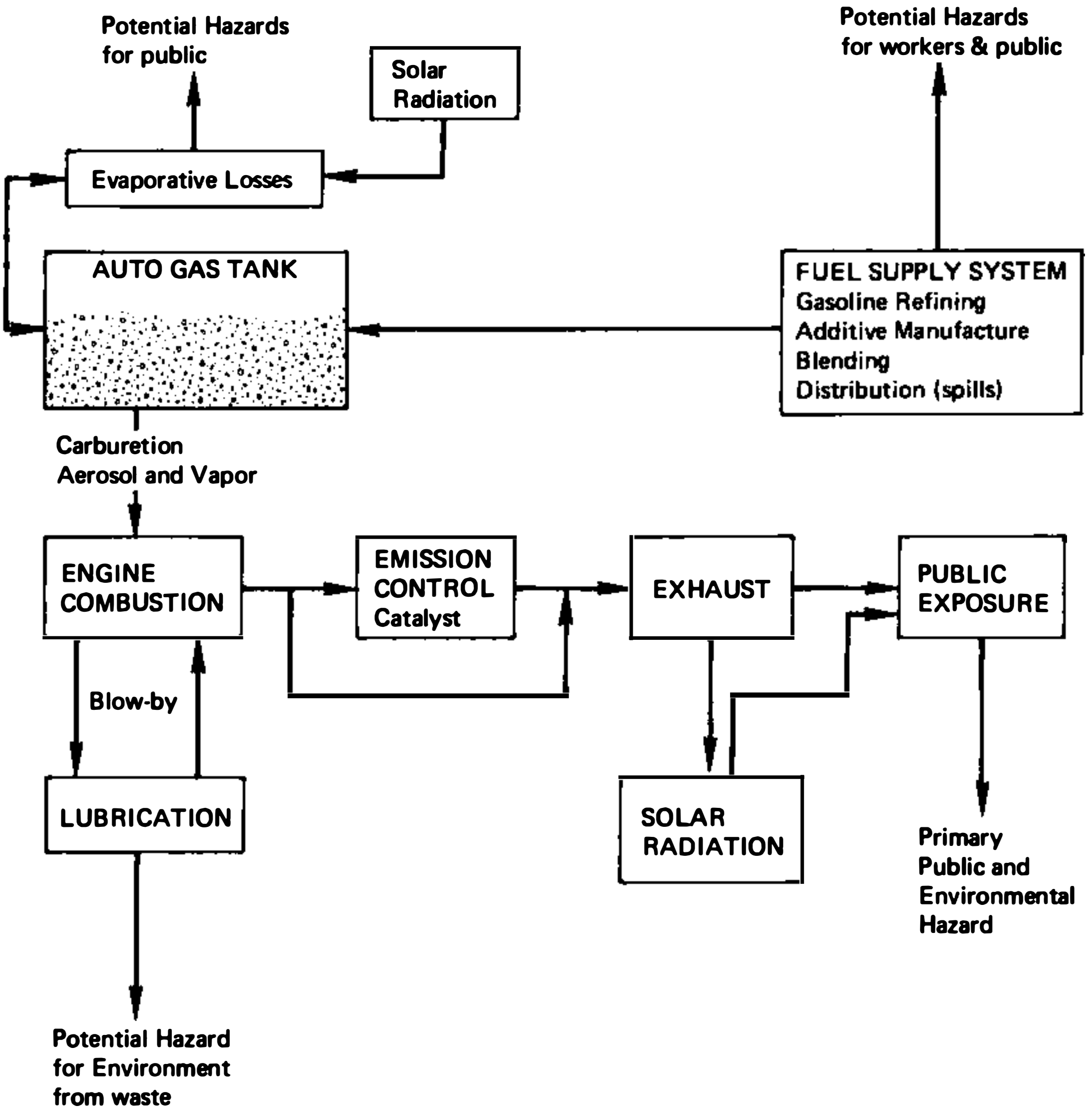
POINTS OF POTENTIAL SOURCES OF POLLUTION FOR ENVIRONMENTAL HAZARDS



APPENDIX II

PROTOCOL FOR EYE IRRITATION TEST (VAPOR) IN ALBINO RABBITS*

Six albino rabbits of the New Zealand strain are used to evaluate the eye-irritating properties of the test material vapors. Air is allowed to circulate through the test material at a rate of 3.0 l/min. The vapor mixture is then allowed to pass over the right eye of each rabbit through a small funnel for a period of 60 sec. The funnel channels the vapor mixture over the eye and helps keep the eye open. The average nominal concentration will be calculated by dividing the weight loss of the test material by the total volume of air circulated during the period of exposure. Such calculations should be checked by analytic measurements if possible.

One, 2, 4, 24, and 72 hr, and 7 days following contact, the cornea, iris and palpebral conjunctiva will be examined and graded for irritation and injury according to a standard scoring system.[15]

It is recommended that the foregoing procedure be validated by an interlaboratory "round-robin" study.

*The Committee expresses its appreciation to Dr. Keplinger for making this unpublished procedure available.

APPENDIX III

COMPOSITION OF FUEL ADDITIVES

About 325 commercial fuel additives had been registered up to 31 December 1972. The additives fall into several functional classes, such as anti-knock compounds, antioxidants, surfactants, and deposit modifiers. Anti-knock compounds contain materials such as tetraethyl lead; the antioxidants are made up of hindered phenols, phenylenediamines, and metal deactivators; the surfactants contain various aliphatic amines, carboxylates, amine carboxylates, and amine phosphates and the deposit modifiers include shortchain halogenated hydrocarbons. Other functional classes are also listed.[20] Anti-knock compounds and smoke suppressants are discussed in recent NAS reports on lead and manganese.[45,46] Thus the relatively large number of commercial fuel additives fall into a relatively small number of basic chemical types. Information provided by the EPA indicates that fuel additives can be divided into about fifteen chemical classes, set forth in the first table. This table also shows the relative frequency of use of each chemical class. The second table lists the fuel concentrations of antioxidants, surfactants, and deposit modifiers.

Chemical Classes and Relative Usage Indices

Chemical Class	Number of Compounds in Each Chemical Class	Number of Additives Containing a Compound From Each Chemical Class
Lead Compounds	6	95
Alkyl Halides	2	79
Azo Naphthols	22	67
Amines	20	42
Aromatics	5	33
Phenylenediamines	10	32
Alkyl Polyamines	10	30
Alcohols	4	29
Phenols	10	29
Aromatic Phosphates	7	26
Alkyl Phosphates	11	23
Anthroquinones	10	22
Azo Compounds	7	16
Naphthalenes	8	11
Trace Substances	7	10

APPENDIX III (cont'd)

Fuel Additives - Composition, Concentration and Usage of Antioxidants, Surfactants, and Deposit Modifiers

Antioxidants

Type	Use	Concentration in Fuel ppm
Hindered phenols	Prevent peroxides	5-20
*Phenylene diamines	Prevent peroxides Prevent polymerization	5-20
Metal deactivators	Chelates copper	1-10

Surfactants

Type	Use	Concentration in Fuel ppm
Amines $R-NH_2$ R-aliphatic N-may be primary, secondary or tertiary	Detergent	40-300
Carboxylates $RCOO^-$ $R-C_{16-18}$	Deicing - Not necessary with air preheaters	40-150
Amine carboxylates $R-C_{16-18}$ $RCOO^- {}^+NH_3R'$	Anti-rust	5-20
Amine phosphates $RNH_3^+PO_4R'$	Improve fuel distribution	40-150

Deposit Modifiers

Type	Use	Concentration in Fuel ppm
Alkyl halides $ClCH_2-CH_2\ Cl$ $BrCH_2-CH_2\ Br$		1 atom Cl) per atom Pb ½ atom Br)

* The antioxidants and surfactants are all relatively nonvolatile organic compounds thought to be largely combusted. The various aromatic and aliphatic amines probably undergo more complete combustion than those containing only hydrocarbons.

APPENDIX IV

COMPOSITION OF FUELS

The following tables list the ranges of physical properties and composition for motor gasolines and diesel fuel. The data were acquired in private communications from Bureau of Mines surveys and Exxon Research and Engineering.

Motor Gasoline

A. Vapor Pressure

	Summer Aver. range	Winter Aver. range
1. Reid vapor pressure, (psig @ 100°F)	9 (7-11)	12 (9-15)
2. Distillation curve, ASTM		
50%	200-220°F	170-250
90%	310-350°F	310-374
Final boiling point	∿ 400°F	395-437

B. Composition

1. Hydrocarbon class*, average % by volume (range)

	Premium (100 RON)		Regular (94 RON)	
	Summer	Winter	Summer	Winter
Aromatics	29 (23-36)	34 (26-40)	25 (19-30)	31 (22-40)
Olefins	7 (3-10)	7 (1-14)	7 (2-14)	9 (3-20)
Saturates	64 (54-74)	59 (48-66)	68 (64-76)	60 (51-64)

2. Lead content 2.4-2.7 g Pb/gal

3. Carbon no. range = 4-11

4. Polynuclear aromatics, as benz(a)pyrene ≈ 0.3 - 0.4 ppm

5. Sulfur is known to be present but quantitative data were not available to the Committee.

* Northeastern U. S. compositions

APPENDIX IV (cont'd)

Diesel Fuel

A. Properties

	Minimum	Maximum
1. Flash point, °F	144	194
2. Pour point, °F	-40	15
3. Cloud point, °F	-20	24

4. Distillation curve, ASTM

	Aver.	Range
50%	498°F	456-533
90%	579°F	536-628
Final boiling point	626°F	582-698

B. Composition

1. Hydrocarbon class*, average % by volume

Aromatics	35	(alkylbenzenes, 2-3 ring aromatics)
Olefins	1-2	
Saturates	64	(n-Paraffins cycloalkanes)

2. Carbon no. range = 10 - 19

3. Polynuclear aromatics, as benz (a) pyrene $\approx$ 0.03 ppm

4. Information on sulfur content was not available to the Committee.

* Northeastern U. S. compositions

APPENDIX V

EXAMPLES OF THE CLASSIFICATION SCHEME AND RATINGS

The toxicity hazard rating system presented here is adapted from one recommended by the Committee on Toxicology of the NRC to the U. S. Coast Guard. It is based upon absolute determinations of acute toxicity rather than upon a relative rating such as proposed in this report for auto exhausts. This scheme may be useful for describing the toxicity hazards associated with uncombusted fuels and fuel additives. Relatively brief, isolated exposures are assumed.

Outline of Rating System

Grade	Vapor Irritants	Liquid or Solid Irritants	Poisons
0	No effect	No effect	No effect
1	Slight effect	Causes skin smarting	Slightly toxic
2	Moderate irritation; temporary effect	First-degree burns, short exposure	Intermediate toxicity
3	Irritating; cannot be tolerated	Second-degree burns, few minutes exposure	Moderately toxic
4	Severe effect; may do permanent injury	Second-degree and third-degree burns	Severely toxic

a. Vapor irritants

The hazard rated here is that presented by chemicals which are gases, or which emit vapors or fogs irritating to the skin or the mucous membranes of the eyes, nose, throat, and lungs. The grade assigned is based on the likelihood of developing injury including a consideration of volatility and injurious concentrations and the severity and permanence of that injury.

This hazard is based on the effect of exposure to vapors or fumes evolved from the chemical, and not to splashes of the liquid itself. A nonvolatile chemical with a low rating may still cause severe damage if splashed into the eyes, and is rated accordingly as a liquid or solid irritant. This rating does not include the potential hazard of suffocation because of displaced air as might be encountered in a confined space.

Grade 0 Nonvolatile materials or vapors which are not irritating to the eyes and throat.

Grade 1 Materials that cause a slight smarting of the eyes or respiratory system if present in high concentrations.

Grade 2 Materials with vapors that cause moderate irritation, such that humans will find high concentrations unpleasant. The effect is temporary.

APPENDIX V (cont'd)

Grade 3 Moderately irritating volatile materials, such that humans will not usually tolerate moderate or high vapor concentrations.

Grade 4 Severe eye or throat irritants, vapors which are capable of causing eye or lung injury, and which are intolerable even at low concentrations.

b. Liquid or solid irritants

Materials in this category are rated with regard to their tendency to chemically burn or irritate human skin from contact in the liquid or solid state. Substances that burn the skin are usually very severe in their effect on the eyes. Hence materials given a high rating in this column will usually be painful and injurious if splashed into the eyes. In most cases, volatile materials that evaporate rapidly are less hazardous than less volatile ones that remain in clothing or on the skin. Ratings are to be increased one grade for materials known to cause an allergic reaction.

Dermal effects from prolonged or repeated contact have not been considered.

Grade 0 No appreciable hazard. These materials are practically harmless to the skin. Included are certain very volatile compounds that evaporate quickly from the skin.

Grade 1 Minimum hazard. Usually includes materials that will cause smarting and reddening of the skin if spilled on clothing and allowed to remain.

Grade 2 Materials that cause smarting of the skin and first-degree burns on short exposure and may cause second-degree burns on long exposure.

Grade 3 Fairly severe skin irritants, usually causing pain and second-degree burns after a few minutes of contact.

Grade 4 Severe skin irritants, causing second- and third-degree burns on short contact and very injurious to the eyes.

c. Chemical poisons

The systemic toxicity hazards from chemicals, that is, chemicals that enter the body through inhalation, oral ingestion, or skin penetration and cause bodily harm are classified here. Volatile chemicals producing toxic effects by inhalation are of the most concern; chemicals toxic by skin absorption are of less concern. Chemicals which are toxic only by oral ingestion usually are not given a high hazard rating, except in a few cases where severe injury may occur.

APPENDIX V (cont'd)

Many parts of the body may be affected when exposed to chemicals, all of which are considered here. Chemicals are rated as health hazards if they are anesthetics, narcotics, or have a cumulative toxic effect, as well as if they are acutely toxic. However, protecting the general public from fuels and fuel additives *per se* is primarily a concern for acute, rather than cumulative toxicity, and hence acute toxicity is given greater weight in the ratings.

Grade 0 No likelihood of producing injury.

Grade 1 Minimum hazard; includes most chemicals having threshold limit values above 500 ppm.

Grade 2 Some hazard, typically having threshold limits of 100 to 500 ppm.

Grade 3 Moderately hazardous chemicals.

Grade 4 Severely hazardous chemicals usually having threshold limits below 10 ppm.

APPENDIX VI

COMMENTS ON GENERATION OF EXHAUST EMISSIONS

Some special comments are needed on subject of generating emissions. The toxicologist needs a procedure for generating emissions from engines operating on a fuel to which additives have been introduced. The procedure must also provide a representative distribution of potentially toxic compounds so that incremental toxicity can be determined. Such procedures should not be unduly complex.

It is recognized that different engine families exist and one or more test procedures may be needed. The batch process type includes gasoline, diesel and stratified charge. They may employ either reciprocating or rotary mechanisms. The continuous burner type includes turbine, jet stirling and steam. Various fuel additives are used or may be used in each of these types.

The Committee recognizes the importance of different engine emission control systems and exhaust treatment control systems to the amount and distribution of emissions. Flexibility and judgment must be used in engine fuel and cycle selection for testing. A typical engine emission control system should be employed for standard tests within each engine-emission control system. Where variations in exhaust treatment systems are suspected to change significantly the distribution of emissions, additional tests should be made with the alternate systems. The possible incremental toxicity of principal additives for a given engine type should be evaluated, with that type being used as the emission source.

Most fuel additives can be evaluated in a standard engine with a standard fuel. Where the gaseous emissions are of principal concern (ashless additives, for example) a medium load, steady state engine test might be used. Since most future fuel additives are expected to be of this type, a steady engine test might become the predominant one. Where incremental toxicity from liquid aerosols or particulates is suspected, transient operation is desirable. An example is the federal exhaust test cycle, unless the additive being tested is used in an engine normally run under steady conditions. When measuring particulates or aerosols, dilution is necessary to avoid condensation. The dilution must be controlled when determing particulate or aerosol effects because the size distribution is affected by dilution.

The Committee emphasizes the desirability of a simple emission source such as a laboratory burner system. No laboratory system is known which correlates with engine exhaust, and such a study seems a worthy research effort. The use of a laboratory burner system may be more realistic for the steady burner type engines.