

## MEETING REPORT

### Epidemiological Research on the Relationship of Exposure to Diesel Emissions and the Development of Respiratory Cancer

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A meeting was held at Luerhof House, Kampen, on the Island of Sylt, Germany, on June 22-23, 1982, to discuss the relationship between general air pollution and respiratory cancer. More specifically, discussion focused on the risk posed by exposure to diesel emissions and the need for research to more adequately define and assess it.

I. T. T. Higgins reviewed the evidence on general air pollution and respiratory cancer. He pointed out that the earlier beliefs of the 1950s that pollution was important now seemed unlikely. At most, it seemed possible that general air pollution might explain up to 5% of all lung cancer. The overwhelming majority of cases were attributable to cigarette smoking with a small, but important fraction being due to a variety of specific occupational exposures. There were few studies which permitted any conclusions about the role of diesel emissions on lung cancer to be drawn. Of the three studies reviewed by the NAS-NRC Health Effects Panel of the Diesel Impacts Study Committee, only one—the Raffle London Transport investigation as followed by Waller (8)—was sufficiently sensitive in terms of both numbers and length of follow-up to permit a reasonably confident conclusion of no excess risk from diesel exposure. Two additional studies, one of heavy equipment operators conducted by Milby and his colleagues and the other of railroad workers conducted by Schenker and Speizer, are in progress. Preliminary accounts of the former do not appear to suggest any increased lung cancer risk from diesel emissions, whereas a pilot study from the latter has suggested a possible small excess risk. To what extent this risk may be due to confounding by asbestos exposure or by cigarette smoking is at present uncertain. Clearly, further analyses and more detailed presentations of the data are awaited with interest.

R. E. Waller presented a series of comments regarding associations between emissions from diesel engines and lung cancer. He noted that:

(a) There has never been any indication from trends or area contrasts in lung cancer mortality that diesel fumes might be implicated. The rising trend in lung cancer seen in so many countries during this century started before diesel engines came into common use, and, at least so far as males are concerned, the trend

has now been reversed (notably in the United Kingdom), even though the use of diesel engines has continued to rise sharply.

(b) Although some early studies indicated the presence of "classical" carcinogens such as benzo[a]pyrene in diesel exhausts, emissions were only notable with gross maladjustment. Otherwise, diesel emissions of such polycyclic aromatic hydrocarbons were generally fewer than those from comparable (uncontrolled) gasoline engines, reflecting the greater efficiency of combustion in the diesel engines.

(c) In general, the amounts of polycyclic aromatic hydrocarbons present in particulate matter from either diesel or gasoline engines are much smaller than those in smoke from incomplete coal combustion. Thus, in the United Kingdom in particular, open coal fires have, in the past, been far more important sources of these compounds than motor vehicles of any kind. With the elimination of such fires in major cities, motor vehicles make an appreciable contribution to the residual amounts of polycyclic aromatic hydrocarbons in the air, but concentrations are very small compared with those seen when and where coal fires were in use.

(d) While it would be misleading to suggest that any specific compound, such as benzo[a]pyrene (BaP), could be regarded as an index of carcinogenicity of any form of pollution or of cigarette smoke, it is of some interest to note that with a typical BaP concentration of about 2 ng/m<sup>3</sup>, as present in cities today with a reasonable degree of pollution control, the daily intake for an adult would be around 30 ng/m<sup>3</sup>, which is of the same order of magnitude as that from a single cigarette in the upper ranges of tar yield.

(e) The more recently developed short-term mutagenicity tests indicate the presence of some activity in extracts from diesel emissions that is not accounted for in terms of the polycyclic aromatic hydrocarbons. This could indicate effects, possibly extending to carcinogenic effects, of further classes of compounds, but this is not a unique finding for diesel emissions; it also applies to a wide range of other materials, including uncontrolled gasoline engine emissions and cigarette smoke. It is difficult at this stage to extrapolate such findings to real situations with the normal levels of exposure to the various smokes. Results of animal inhalation experiments in progress at various centers may throw further light on this.

(f) The few studies of groups exposed occupationally to diesel fumes reported so far do not provide any real evidence of lung cancer risk. One reservation about this is that it has not, in general, been possible to determine whether the smoking habits of the groups studied varied from the norm. While smoking undoubtedly has an overwhelming effect compared with any that might be attributed to air pollution of any kind, it seems unlikely that the picture obtained to date among groups with occupational diesel exposures would be changed substantially by variations in smoking habits.

(g) If the matter is to be pursued further there is a need to concentrate first on populations with special exposures. These are, however, very difficult to define, since diesel emissions form only one component of the general mixture of air

pollutants to which the general population is exposed, and even among occupational groups (such as maintenance men in garages), there may be a mixture of diesel and gasoline emissions, in addition to the background from other sources. Bus garage workers have been studied in London. This work continues, with provision for follow-up to death even after leaving service. While emissions in such garages are confined to diesel engines, it is only in the more poorly ventilated ones that exposures are likely to be appreciably greater than in the general population. Mine and railway workers have also been studied, but in these cases, the engines in question are still further removed from the light-duty engines that are of current concern. There are, in fact, few countries where diesel-engined road vehicles have been used widely enough and long enough to have had any real impact of exposures on any sections of the population yet; the United Kingdom and Germany may have the longest histories.

The importance of biochemical measurements in persons exposed to diesel emissions was stressed by D. Hoffmann and others. Hoffmann suggested that two approaches were possible. Blood serum might be analyzed for nitropolynuclear aromatic hydrocarbons (nitro-PAH) as indicators of exposure to direct-acting carcinogens; urine might be analyzed for *N*-nitrosoproline (NPRO) as an indicator for *in vivo* formation of carcinogens from compounds present in diesel exhaust.

Nitro-PAH, especially 2-nitronaphthalene and 1-nitrophenanthrene, are highly genotoxic agents which thus far have been detected in diesel exhaust but not in other nonoccupational pollutants (1,2). The *in vivo* formation of carcinogenic *N*-nitrosamines from endogenic and/or environmental amines and nitrogen oxides is most appropriately assayed by determining NPRO in urine. NPRO serves as a surrogate for carcinogenic *N*-nitrosamines formed *in vivo*. It is not carcinogenic; more than 95% of the compound is excreted in the urine in unmetabolized form (3,4). Hoffmann noted that GC-ECD or GC-TEA methods are now available for the trace analysis of nitro-PAH and NPRO. But these methods are cumbersome and do not meet the required sensitivities of  $10^{-10}$  g/ml. They are, therefore, not suitable for analysis of the large volume of samples required for population studies. Radioimmunoassays need to be developed to meet the above-cited requirements.

Much of the discussion focused on the types of epidemiological studies which could be conducted to illuminate the relationship between exposure to diesel emissions and the development of lung cancer. The suggestion was made that a comparison of lung cancer rates in counties with and without major highways might be one approach. The group agreed, however, that even if counties could be differentiated in this simple manner, other important differences between the residents of these counties, which could not be controlled, would make any apparent associations with highways impossible to interpret. Indeed there was consensus that the time for correlational studies of this kind is now past and that attention should be directed toward establishing exposures, confounding factors, and outcomes in individuals if any significant advance in understanding is to be made.

Places where pollution was believed to be an important problem were discussed as possible locations for further studies of air pollution. A. Kafatos produced evidence that suggested pollution in Athens, though declining, was still relatively high and varied markedly from area to area. Mexico City, São Paulo, and Bombay were other cities which were thought to justify further consideration for studies of air pollution.

Various occupational groups in which studies might be undertaken were discussed. Apart from bus mechanics, railroad employees, and heavy-duty vehicle equipment operators, who are already under study, drivers of dieselized vehicles, for example, taxi or truck drivers, employees at service stations, military personnel in the army motor pool, airplane mechanics, naval personnel on diesel-powered ships including submarines, and underground miners of metal ores, coal, and salt, were thought to be suitable for further exploration.

Two types of study were considered by most members of the group to be likely to be worthwhile. The first of these is a prospective study of special exposure groups if these can be unequivocally shown to be exposed to higher concentrations of pollutants from diesel emissions than other persons in the community. This is a proviso which has often been overlooked. As Waller indicated, the London bus mechanics are now thought to have been exposed to appreciably higher concentrations of diesel emissions than other people only when they worked in poorly ventilated areas of the garages. Before launching a large, prospective epidemiological investigation, it is important to show that exposures in groups to be compared are in fact different. It is not sufficient to suspect that they may be. If possible, personal monitoring should be incorporated into the design of the study. Attempts should also be made to identify and measure biological markers (nitro-PAH and *N*-nitrosoproline) as indicators of exposure to diesel exhaust constituents, as suggested by Hoffmann.

The second type of study for which there was consensus was a comparison of lung cancer cases with an appropriate comparison group. The main objective of this would be to assess present and past urban living and thus estimate exposure to pollutants while allowing for smoking habits, occupational exposures, socioeconomic status, and mobility. N. Pelz and E. L. Wynder urged the continued collection of data from the various cancer case/control groups now being studied by the American Health Foundation. Special consideration is already being directed to smoking, occupation, and residence in these ongoing studies. Categorization of cancers by histological type is also being carried out in these studies.

The desirability of linking case-comparison studies to a population base was also discussed. This can best be accomplished by identifying cancer cases through a population-based cancer registry. In this circumstance, comparisons of the determinants of lung cancer can most readily be carried out by comparing lung cancer cases with other types of cancer identified by the Registry. The possibility of defining a more representative sample of the community served by the cancer registry to serve as the control or comparison group also should be considered.

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