EXECUTIVE SUMMARY

ARB CONTRACT A4-064-33

THE ROLE OF NO_2 AND O_3 IN CANCER METASTASIS AND IN SYSTEMIC ADVERSE EFFECTS

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The presence of pollutants in the environment, especially those with carcinogenic properties, has been of great concern to environmental health scientists and air quality regulatory agencies. In view of this, many studies have been directed toward the identification of cancer-causing agents in the air we breathe. However, the problem of cancer involves not only the development and presence of cancer cells at a primary site, but also the ability of these cells to migrate, seed, proliferate and develop secondary cancer masses or metastases in distant organs and tissues. Considering the fact that a significant segment of the population in the United States is already affected by cancer, together with the probability that one in three individuals will develop cancer, a real question arises as to the role of environmental air pollutants in dissemination of cancer cells and the development of metastases. Little attention has been paid to the possibility that inhalation of a noxious air pollutant could facilitate the spread of already existing cancer cells.

Since the presence of circulating, or blood-borne, cancer cells is well recognized in cancer patients, it is important to identify extrinsic factors which may influence the survival of these cells and development of metastases. Utilizing an animal model and a common skin cancer (malignant melanoma), our studies under previous contracts have demonstrated that inhalation of 0.3 - 0.8 ppm of nitrogen dioxide (a common air pollutant) will faciliate blood-borne melanoma cell metastasis to the lungs of exposed animals. Exposure to ozone, another common air pollutant, does not exhibit this phenomenon. Studies under present contract have demonstrated that exposure to a combination of nitrogen dioxide and ozone at 0.35 ppm and 0.15 ppm, respectively, results in facilitation of blood-borne melanoma cell metastasis. One

would suspect that this is due to harmful nitrogen dioxide effects on some biological systems in these animals. Of the many possible cellular systems that nitrogen dioxide may affect, the defense system and the blood capillaries in the lung would be the most likely targets, and damage to these cells could, in part, account for these findings. For this reason the major effort of this contract was to identify the affected cells of these systems utilizing 0.4 ppm intermittent nitrogen dioxide exposure, a level which may be encountered in Los Angeles on a smoggy day.

In the defense system we have several cell types which play significant roles in protecting the body from development and spread of cancer. Some of these cells are known as white blood cells, and a special white cell called a "lymphocyte" is particularly important in defense against cancer and infectious diseases. Our studies utilizing special immunological techniques have indicated that certain lymphocytes may be damaged by inhalation of nitrogen dioxide to the extent that their defense functions are seriously impaired. Damage was also observed in cells lining the blood capillaries. The latter damage was detected utilizing an electron microscope, which permits the examination of the cells under very high magnification. The increased incidence of blood clots in lung capillaries of exposed animals was another indication of capillary damage.

The most important aspect of these experiments is the fact that inhalation of ambient concentrations of nitrogen dioxide can enhance or facilitate the dissemination of cancer, particularly the circulating cancer cells, by affecting different host tissues and cells. These findings are highly relevant to human health because alterations in the immune system or blood capillaries, the focus of these studies, are frequently associated with diverse human diseases. If indeed these or similar events are taking place in humans, as some epidemiological studies suggest, the

control of nitrogen dioxide levels in urban areas may be very critical to human health. The exposure may lead not only to increased and accelerated dissemination of cancer, but to several other serious health problems, such as enhancement of atherosclerosis development, decreased resistance to viral and bacterial infections, and expression of other opportunistic organisms. Since the function of the body's defense system depends upon a very fine balance among the cells of the defense system, it is imperative to recognize extrinsic substances, including air pollutants, which may affect these cells. The knowledge of pollutant effects on specific cells of the defense system could become a very sensitive indicator of adverse effects, and findings from such studies should play a role in decisions on air quality standards. In view of this, more expanded studies are needed to establish how seriously different air pollutants may affect our defenses.