A Possible Nitrogen Oxide–Nitrosamine–Cancer Link

by
DAVID H. FINE, FIROOZ RUFEH, and DAVID LIEB
Thermo Electron Corporation,
85 First Avenue, Waltham, Mass. 02154
and
SAMUEL S. EPSTEIN
School of Medicine
Case Western Reserve University
Cleveland, Ohio 44106

The United States Environmental Protection Agency (EPA) has recently recommended (FEDERAL REGISTER, 1973) that the nitrogen dioxide (NO_2) emission standards be relaxed. The decision is based exclusively on the short term effects of the Chattanooga and other studies (PEARLMAN et al 1971) and does not consider the long term effects of NO_x (nitric oxide and nitrogen dioxide) exposure. There is a growing awareness that N-nitrosamines, for which NO_x is a precursor, are a major class of carcinogens that are likely to be causally related to human cancer (LIJINSKY AND EPSTEIN 1970).

From studies on tobacco smoke, nitrogen oxides are known to be readily absorbed by the body during inhalation (BOKHOVEN AND NIESSEN 1961). Furthermore, it has been shown (NEURATH 1972) that equimolar mixtures of nitrogen dioxide and nitric oxide (the two major oxides of nitrogen present in the environment) are capable of nitrosating secondary and tertiary amines to form the highly carcinogenic N-nitrosamines.

The efficiency of *in vivo* conversion of NO_x to N-nitrosamines is unknown. If the conversion were assumed to be 10% efficient, the amount of say, diethylnitrosamine, which could be formed from 'clean' air containing 100 $\mu g/m^3$ of NO_2 is 4 µg per kg body weight per day*. This is to be compared with a dose of 75 µg/kg/day for rats which has been clearly demonstrated to be carcinogenic and above the apparent "no-effect" level (PREUSSMANN 1972).

It must be concluded, therefore, that absorption of nitrogen dioxide and nitric oxide and its subsequent conversion to N-nitrosamines, even from levels of nitrogen dioxide recommended by EPA, could pose significant public health hazards in general and carcinogenic hazards in particular.

---

* The assumptions used in the calculation are that an average man weighs 120 pounds, and takes 14 breaths per minute, each of 300 cc in volume. The ratio of NO to NO_2 in urban air is assumed to be unity (a conservative value).

Bulletin of Environmental Contamination & Toxicology,
Vol 11, No. 1 © 1974 by Springer-Verlag New York Inc.

The NO_x - nitrosamine - cancer link, while admittedly speculative, is consistent with all available current scientific knowledge.

REFERENCES

BOKHOVEN, C., and H. J. NIESSEN: Nature 192, 458 (1961); NORMAN, V., and C. H. KEITH: Nature 205, 915 (1965).

Federal Register, Washington, pp 15174-15183, June 8, 1973.

LIJINSKY, W., and S. S. EPSTEIN: Nature 225, 21 (1970).

NEURATH, G. B., in N-Nitroso Compound Analysis and Formation, P. BOGOVSKI, R. PREUSSMANN, and E. A. WALKER, Ed. (International Agency for Research on Cancer, Lyon, France) pp 134-136 (1972).

PEARLMAN, M. E., J. F. FINKLEA, J. P. CREASON, C. M. SHY, M. M. YOUNG, and R. J. M. HORTON: Pediatrics, 47, 391 (1971).

PREUSSMANN, R., in N-Nitroso Compounds Analysis and Formation, P. BOGOVSKI, R. PREUSSMANN and E. A. WALKER, Ed. (International Agency for Research on Cancer, Lyon, France) pp 6-9 (1972).