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OXIDES OF CARBON AND NITROGEN IN CIGARETTE SMOKE

Direct Hazards of Oxides of Nitrogen

Study of the available literature indicates that only a limited amount of information is available concerning the proportions of those oxides in cigarette smoke. Haagen-Smit[1] have distinguished between nitric oxide (NO) and nitrogen peroxide (NO_2) and record quantitative figures varying between 145 to 655 ppm. Bokhoven and Niessen[2] have found NO plus NO_2 at the level of 170 to 210 ppm, with NO_2 being 80 to 120 ppm. The smoking conditions used by these people are sufficiently similar to indicate the reasonableness of these figures.

Absorption of the Oxides of Nitrogen

Bokhoven and Niessen[2] showed that the oxides of nitrogen are absorbed to a large extent (approximately 87 - 96%) with inhalation experiments. Penetration into the lungs has been considered by la Belle[3] who considers it to be a 100%, but suggests that penetration is significantly reduced in the presence of liquid or solid aerosols of lower penetrative power. The penetration of liquid and solid aerosols into the lungs has been studied by a number of workers [4-6]. There is general agreement that nasal retention is negligible below 1μ, increasing to 100% at 5μ; retention in the alveoli decreases as the particle size falls below 1μ, reaching a minimum at approximately 0.2μ, and increasing again for still smaller particles. There is also some evidence that the alveolar retention falls off for particles in excess of 1μ. The maximum alveolar deposition amounts to 50 to 60% with the minimum being roughly 20%. From the various published figures of cigarette smoke particle size, it is likely that the deposition in the alveoli would be of the [illegible] of 20 to 50%.

It therefore appears likely that the penetrative effects of the oxides of nitrogen in cigarette smoke may be reduced.

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Toxicity

The basic effects of nitrogen oxides have been discussed by Pieters[7] whose findings are summarised:

"Nitrogen oxides react with moisture forming nitrous and nitric acids in the mucous membranes of the respiratory organs, causing irritation and coughing, while damage to the alveolar cells results in oedema which involves the hazard of suffocation. The action on the blood is shown in the formation of methaemo-globin, which being unfit for oxygen transport results in cyanosis. Oedema is responsible for the fatal cases. Repeated inhalation of nitrogen oxides in small concentrations gives rise to serious chronic effects."

Direct Hazards of Carbon Monoxide (CO)

A survey of the literature suggests that carbon monoxide is present in cigarette smoke to the extent of 4-6%.

Absorption

Bokhoven and Niessen[2] showed with inhalation experiments that carbon monoxide is absorbed to a large extent (82%), and, although laBelle has not specifically considered the monoxide, it is probable that the gas has a high penetrative power which in the presence of smoke is reduced. In the reviews of both Proosdij and Larson it is pointed out that a number of earlier workers had obtained similar values for monoxide absorption; but the method used has been criticised as being inaccurate. The poisonous action of carbon monoxide is based on its affinity for haemoglobin with which it forms a relatively stable compound, the affinity is 300 times that for oxygen. Direct measure of the carboxyhaemoglobin in the blood has generally shown the absorption level in the lungs to be considerably lower than expected from other type measurements (those of Bokhoven and Niessen).

There is considerable data regarding carboxyhaemoglobin (COHb) levels in

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smokers and non-smokers which is well summarised in the reviews of Proosdij and Larson. In general, non-smokers have COHb values of 1% or less while those for smokers may rise to 5-10% during smoking, falling rapidly to 2% within half an hour. The rise depends on the degree of inhalation. There is, however, very little evidence on the rate of absorption or desorption of carbon monoxide. Oberstag and Scoch-Karter[8] found that the in vitro monoxide absorption curve of the blood of habitual smokers differed by a quick initial increase from the blood carbon monoxide saturation curve for non-smokers, which was characterised by a flat course in the beginning; these same workers confirmed these findings in in vivo smoking experiments on smokers and non-smokers. A number of comparisons of blood COHb levels reached due to cigarette smoking with those from breathing poluted air have been made[9-11]. It is apparent that while COHb residual levels in smokers may be double those of non-smokers, both levels are very low, and non-smokers exposed to CO in the course of their work or through environment (especially police, garage and blast furnace workers) may well have higher residual COHb levels than heavy smokers. Only in exceptional cases does the COHb level of a heavy smoker exceed 10%.

Toxicity

The basic effect of CO has been discussed by Pieters whose findings are summarised: "The poisonous action of CO is based on the affinity of haemoglobin which is

> 300 times that of haemoglobin for oxygen. The ensuing oxygen difficiency first gives symptoms of headache, dizziness and nausea, still prolonged oxygen difficiency causes irreparable damage to the nervous system and blood vessels which can result in death."

Pieters showed that no observable toxic effects are obtained up to levels of 10% COHb in the blood. It has however been pointed out that this 'safe' level will vary with the individual. Some may be able to absorb considerably more carbon monoxide before any symptoms appear while others may react to levels of 5% or less.

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There has been much discussion in the literature concerning the occurrence of chronic monoxide poisoning. While it has been generally held that there is no such entity as chronic monoxide poisoning resulting from continued exposure to sub-toxic concentrations, and the recent R.C.P. report has concluded from the evidence available that COHb levels attained in smoking are not sufficient to have clinical effects under normal circumstances, even though these levels may reach 10% during puffing of a cigarette, yet this view is not held ununanimously. Gilbert and Glaser[12] consider that chronic carbon monoxide intoxication definitely occurs after prolonged exposure to low levels and is characterised by symptoms and signs that persist between exposures. Roffo[13] feels that while the carbon monoxide detected in cigarette smoke is far below the toxic dose, it causes the state of slow chronic asphyxia which he considers important in the development of carcinomas. Bentley[14] has however concluded that there is no experimental evidence to show that CO is a respiratory carcinogen; on the contrary, partial anoxia has been found not to increase the existence of lung tumours in mice[15]. However, T.M.S.C. has recently been advised that Dr. A. C. Allison of the National Institute of Medical Research has shown that carbon monoxide can cause lung cancer in experimental animals and that the work is shortly to be published.

During the conference held by the British Occupational Hygiene Society on April 17th 1962, several speakers stressed that the effects of carbon monoxide in low concentrations is virtually unknown and that we should be considering the effects on those most prone rather than those enjoying good health. Cotes (Pneumoconiosis Research Unit, M.R.C.) mentioned that low concentrations of CO produce biological effects which may affect human performance and quoted that there is a significant change in visual threshold at 20 ppm which is the equivalent of only one cigarette.

Maximum Allowable Concentrations for both Oxides of Nitrogen and Carbon Monoxide

As these gases are potentially industrial hazards, maximum allowable concentrations of vapours (M.A.C. expressed as ppm of air per 8 hour day of continuous

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exposure) have been adopted in various countries. The M.A.C. values currently accepted in Britain or U.S.A. are 100 ppm for CO and 25 ppm for NO_2 over an 8 hour working day. The State of California Department of Public Health have suggested a limit of 5% COHb (30 ppm per 8 hours, 120 ppm per 1 hour) which they state as appearing to be as entirely safe for a general population as 100 ppm per 8 hours is for a working population. Copplestone[16] in a discussion of the health aspects of exhaust fumes, points out that diesel exhausts produce NO_2, and gives a M.A.C. for NO_2 of 5 ppm over a 40 hour working week. The M.A.C. for CO is again 100 ppm.

Values used by Bokhoven to represent M.A.C.'s in the atmosphere are based on figures suggested by Riasanov. These values for CO and nitrogen oxides are considerably lower than those currently accepted in Britain or the U.S.A; the Russian figures are 1.7 and 0.05 ppm respectively over 24 hours. Whilst the British-American accepted values are not based on scientific findings but on experience, it might be argued that the Russian figures which are based on levels below which no electrocortical reflex has been observed in a subject during inspiration of short durations provided a more scientific basis. However, there is no evidence that chronic or toxic effects will occur immediately above these Russian limits and their acceptance of a threefold increased allowable level for expiration over 24 hours has no factual basis.

While recognising that the presently accepted British M.A.C.'s may have to be reduced in the light of further knowledge, especially if one considers that such levels should be based on tolerance limits on those most prone rather than on those with average tolerance, we feel that the Russian levels do not at this time provide a realistic basis. If we now accept the British M.A.C. values for CO and NO_2 we find that the smoker of 40 cigarettes daily can inhale almost as much CO as if he breathed air at the M.A.C. for 8 hours but that in order to reach these levels for NO_2 he would have to smoke approximately 1,000 cigarettes in a day.

Indirect Hazards of the Oxides of Nitrogen

Nitrosamines

Recently emphasis has been placed upon the nitrosamines; these are produced by the action of nitrous acid on secondary aliphatic or aromatic amines. Since both nitric oxide, nitrogen peroxide and water are present in cigarette smoke, there is a likelihood of forming nitrous and nitric acids. Regarding the presence of secondary amines in cigarette smoke some published information is available, certainly diethylamine and nor-nicotine are present in some smokes and the latter could form the N-nitroso-nornicotine which is a yellow liquid having a boiling point of 190°C at 0.5 mm pressure.

It is interesting to postulate that the lack of information on the presence of secondary amines in smoke may be due to the fact that they have formed nitroso derivatives and as such exist in the neutral and not basic fraction of cigarette smoke.

Therefore, it seems feasible that nitrosamines may be present; taking the physical characteristics of a relatively common nitrosamine-dimethylnitrosamine of boiling point 153°C it could be postulated that such material could exist in both the particulate and vapour phase of cigarette smoke.

C-Nitroso Compounds

Although it is probable that these compounds have no biological activity it is of interest to note here that nitrous acid will also react with tertiary aromatic amines of phenols to give C-nitroso compounds. Perhaps more important is the gas phase reaction of nitric oxide with free radicals. Gaseous free radicals produced by thermal degradation can react directly with nitric oxide to form C-nitroso compounds. These compounds are reasonably stable at elevated temperatures (for example, isopropyl nitroso compounds and butyl nitroso compounds boil at 230 -

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280°C and 370 - 410°C respectively).

Indirect Hazard of Carbonmonoxide

Of considerable interest recently has been the concern regarding possible hazards of nickel. It is known that nickel refinery workers are prone to lung cancer, the metal being transferred to the respiratory system as nickel carbonyl which, being unstable, results in the deposition of nickel in a highly active form on the respiratory mucosa. Sunderman has been engaged in a study of the implication of nickel as a carcinogen in tobacco smoke. He has found that American cigarettes can contain up to 2 mg. of nickel per cigarette and indicates that as much as 20% can be transferred to the smoke stream. Nickel has a melting point of 1455°C and a boiling point of 2900°C and on first sight it seems unlikely that 20% can be transferred directly as a result of the temperature existing in the burning cigarette. Consequently, it is feasible that carbon monoxide reacts with reduced nickel to form the nickel carbonyl (boiling point 43°C) which is then transferable. There may be some doubts concerning this maximum since nickel carbonyls are easily decomposed, nevertheless it is worthy of consideration.

Recommendations

1. NO_2 is considered to be five times more toxic than NO and the M.A.C. for NO_2 is 25 ppm. The amounts of nitrogen oxides present in cigarette smoke are so low that one would have to smoke approximately 1,000 cigarettes daily to reach this M.A.C. It is therefore difficult to see that there can be any direct hazard from these oxides in smoke and no action is proposed.
2. The oxides of nitrogen may well be an indirect hazard as a result of their reactivity with secondary amines to produce nitrosamines. Consequently it is proposed that work should be carried out to determine whether or not nitrosamines exist in cigarette smoke.

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3. The M.A.C. value for CO is 100 ppm and a smoker of 40 cigarettes daily may possibly reach this level. The chronic effects of CO absorption may well have been underestimated in the past and it is not unlikely that biological effects may be produced which affect human performance. Therefore, it seems politic to consider feasible means of reducing carbonmonoxide in smoke. The work carried out by the Battelle Institute, although not well conceived, showed that efficient filtration of CO may be difficult to achieve. Therefore it seems that consideration should be given to the treatment of cigarettes in some way to reduce the proportions of CO formed, having first studied the variation in yield of CO with smoking parameters etc.

4. The likelihood of the Sunderman figures of a 20% nickel transfer into smoke and the possibility of nickel carbonyl being the conveying agent requires serious consideration. To effectively prevent this will mean the complete removal of carbonmonoxide and this would seem to be unlikely. Therefore, it is suggested, though not falling within the province of this sub-committee, that measurements should be made to determine nickel content and transfer. If these measurements agree with those published by Sunderman then serious consideration should be given to the elimination of nickel.

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