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Toxic Chemicals In Cigarette Mainstream Smoke – Hazard And Hoopla

Alan RODGMAN and Charles R. GREEN, Winston-Salem, NC 27103 USA

These are curious times. The Canadian government has passed legislation that requires cigarette manufacturers to routinely test and publish the amounts of 44 toxic substances in cigarette mainstream smoke (MSS). Following in its northern neighbor's footsteps, the US Federal Trade Commission (FTC) is considering modifications to the US cigarette testing program that will also list toxicants in MSS. Across the Atlantic Ocean, the European Commission has passed a directive that may also follow the North American lead for public disclosure of MSS toxic chemicals for each brand of cigarette sold in the marketplace. United Kingdom authorities have already expressed their intention to follow this mandate.

It is difficult to understand the motivation and value of these existing or potentially forthcoming legislative actions. Although there is near total agreement among the world's scientists that cigarette smoking is a health hazard, few are bold enough to say with credibility which smoke chemicals or classes of chemicals are responsible for the adverse effects. Therefore, if the specialists are unable to interpret the smoke toxicant data, how is the general public to use their newfound knowledge?

The posting of smoke chemical toxicant data is also problematic for the tobacco industry for several reasons. First, no standard analytical methods exist for most suspected toxicants. Second, the listing of smoke toxicant yields may ignite a 21st Century version of the "tar" wars; we have already seen evidence of such competition beginning in the US. Third, and most important of all, no one knows whether or not reducing the yield of one or more publicized MSS toxicant will result in a "less hazardous" cigarette.

Assuming that the current situation is approximately as described above, the authors of this paper will critically examine the existing list of MSS toxicants. We will discard chemicals that are no longer relevant, e.g., DDT, *N*-nitrosodiethanolamine, add known smoke constituents that are glaringly absent, e.g., dioxins, and replace the existing 1950-60s era nonfiltered cigarette MSS yields with those more representative of the present-day marketplace. Data for the Kentucky Reference 1R4F cigarette smoked under standardized smoking conditions, i.e., those established by ISO and the FTC, will be used as a surrogate for the modern-day cigarette whenever possible.

A list of smoke toxicants and their approximate concentrations in today's cigarettes is nearly useless without an appropriate ranking of their relative toxicity. Unfortunately, the toxicological data for ranking importance are available for fewer than 5% of the approximately 4,800 reported smoke constituents. Although neither of this paper's authors presumes to be a toxicologist, there have been several published attempts at ranking smoke toxicants that we will review in our discussion. Specifically, ranking by US OSHA permissible workplace exposure levels, use of USEPA toxicity criteria supplemented with California EPA criteria, and use of the Human Exposure – Rodent Potential methodology and database developed by AMES *et al.* will be reviewed. There appears to be a wide divergence in the permissible exposures allowable in the workplace and those advocated by environmental regulators. Thus, it is expected that rankings such as those mentioned herein will ultimately form the basis of MSS toxic chemical prioritization for either attempts at reduction by product developers or development of standardized analytical methods.

This review of MSS smoke toxicants will also explore the limitations of toxicological evaluations. The toxicological data used in the above ranking are derived wholly from studies of pure compounds. It is highly improbable that extrapolation of bioassay results determined on an individual compound to that compound when it is a component of a mixture as complex as cigarette MSS is valid. For example, several decades of research involved numerous investigators who reported that the benzo[*a*]pyrene content of cigarette smoke condensate (CSC) accounted for only a few percent of the

tumor-bearing animals in the skin-painting bioassay. Subsequently they asserted that the tumorigenic polycyclic aromatic hydrocarbons (PAHs) in CSC could account for no more than 3 to 4% of the tumor-bearing animals. Inclusion of the promoters (phenols) raised the level to about 5%. However, several of the same investigators recently asserted that benzo[*a*]pyrene is one of two smoke components responsible for lung cancer in cigarette smokers.

While much is written about the hundred or so toxic components in cigarette smoke, little is published about the numerous nontoxic smoke components that have been shown in various bioassays to counteract the effects of the toxic ones. In some cases the inhibiting components are also listed as toxic, e.g., nicotine inhibits the mutagenicity of *N*-nitrosodimethylamine; the promoter phenol inhibits the tumorigenicity of benzo[*a*]pyrene; the weakly tumorigenic benz[*a*]anthracene negates the potent tumorigenicity of benzo[*a*]pyrene. On a one-to-one molar basis, many bicyclic, tricyclic, and tetracyclic nontumorigenic PAHs counteract the tumorigenicity of benzo[*a*]pyrene and dibenz[*a,h*]anthracene.

To further illustrate this murky toxicological situation, the history and current knowledge of the importance of tobacco specific nitrosamines (TSNAs) to the hazards of smoking will be reviewed. In brief, these compounds were discovered in tobacco products and found to transfer to MSS (and side-stream smoke). Toxicological evaluations on the pure compounds demonstrated that they are potent carcinogens. Some public health scientists believed that if the levels of TSNAs could be reduced or lowered in MSS, then this would lead to a “less hazardous” cigarette. Once given this assignment, agronomists discovered that at least for flue-cured tobaccos, the levels of TSNAs could be greatly reduced through the use of indirect heating in the curing barns. This was wonderful news. However, toxicologists soon began experiments comparing the toxicity of MSS from flue-cured cigarettes containing high and ultra-low concentrations of TSNAs. It must have been a surprise to these investigators when they could find no significant difference between the toxicities of the two smokes.

It has been asserted that the reduction of the per cigarette “tar” delivery below 15 mg/cig does not reduce the risk from smoking because of the hazard resulting from the higher levels of additives used to maintain consumer acceptability. Although no data in support of this assertion have ever been offered, much data generated during the past decade contradict the assertion. Ingredient addition at the usual level or at levels several times greater than normal did produce some changes in the smoke chemistry but these changes did not result in any adverse biological response as measured in various bioassays to determine mutagenicity, tumorigenicity, etc.

From our review of the literature gathered to prepare this paper, we have come to several conclusions. These include the following:

1. It is possible to prepare a list of the known toxicants in MSS and to prioritize some of them based upon existing biological data. However, for more than 95% of the known constituents in MSS, there are no biological data.
2. Even if there were biological data for most MSS smoke components, extrapolation of this pure-compound knowledge to the biological properties of a mixture containing them is beyond our scientific ability.
3. At our current state of scientific knowledge, no one will ever be able to legitimately claim the development of a “less hazardous” cigarette based solely on the reduction of known toxic chemicals in MSS.
4. The approach of reducing “tar” yields of cigarettes appears in retrospect to be the most practical means of producing a “less hazardous” cigarette, because when product developers reduce “tar,” both the known and unknown toxicants are reduced.
5. The ranked toxicants in MSS contain both gas-phase and semi-volatile constituents that appear to be important determinants of toxicity. Some of these constituents, e.g., *N*-nitrosodimethylamine, phenols, are reduced by triacetin-plasticized cellulose acetate filters. These filters also reduce “tar.” Additionally, it is well known that charcoal-containing filters have a high efficiency for removing carbonyl compounds from MSS. Development of more consumer-acceptable products that reduce gas-phase toxicants appears to be another route to a “less hazardous” cigarette.

Lung Cancer Risk as a Function of Cigarette Design: Filtration, Blend and Yield

William S. SIMMONS, R. J. Reynolds Tobacco Company, P. O. Box 1487, Winston-Salem, NC 27102 USA

Over 50 years have passed since the first epidemiology studies of cigarette smoking and lung cancer risk were published in the U.S. and the U.K. During this time, numerous innovations in cigarette design have resulted in dramatic reductions in cigarette yields as well as changes in yield composition. Epidemiologists have continued to evaluate the lung cancer risk associated with cigarette smoking and several hundred studies—from virtually every continent—have been published that demonstrate that smoking is the major known risk factor for lung cancer. Other studies have addressed the influence of cigarette design on lung cancer risk. Factors such as filtration versus non-filtration, blond versus dark tobacco, machine-made versus hand-rolled and high-yield versus low-yield have been studied in Europe, South America and the United States. These studies are confounded by diversity of lifestyle in subject populations and limited by the scarcity of smokers who have smoked exclusively one type of cigarette. The rapid evolution of cigarette design has made available to the smoker a variety of blended cigarettes in a spectrum of standardized (FTC or ISO) yields, with the result that smokers who have smoked only one style of cigarette over their lifetime are rare. Furthermore, no studies have appeared that compare the more recent ultra-low-yield cigarettes with the more popular medium-yield cigarettes. Nevertheless, the available evidence shows that lung cancer rates are lower in smokers of: 1) filtered versus non-filtered cigarettes; 2) blond versus black tobacco cigarettes; and (3) low-yield versus high-yield cigarettes. More recently, a number of studies have appeared purporting to show an increase in the frequency of lung adenocarcinoma in smokers. Some investigators have attempted to attribute this apparent increase to the advent of the ultra-low-yield cigarette. The available evidence does not support this conclusion. It is more likely that the increase in adenocarcinoma (if it is real and not an artifact of improved diagnostics) is being driven by some lifestyle factor other than smoking. For example, the obesity rate in the U.S. went from 12% in 1990 to 23% in 1998, an increase which has been attributed to higher consumption of fat. Several studies have shown that diets high in fats are associated with adenocarcinoma of the lung. Although the available evidence is imperfect, it consistently suggests that lower-yield cigarettes are associated with lower rates of lung cancer. There remains, however, a need for data on smokers of ultra-low-yield cigarettes.

Less hazardous cigarettes : the dawn of a new era in the history of tobacco

Gio B. GORI, The Health Policy Center, 6704 Barr Road, Bethesda, MD 20816 USA

The 1964 report of the US Surgeon General left lingering doubts about a causal connection of smoking and diseases. Because of these doubts and the overwhelming prevalence of smoking, the US Congress could not ban cigarettes, and opted for the requirement to grade cigarettes for tar and nicotine yield. Shortly thereafter, in 1968 the National Cancer Institute in the USA began the Smoking and Health Program (SHP), aiming at developing less hazardous cigarettes (LHCs) with the cooperation of the major US cigarettes manufacturers.

By the mid '70s the SHP had tested cigarette modifications that reduced the yield and the specific toxicity of smoke. At the same time, worldwide research started making clear that nicotine was not the problem, and that improved cigarettes should yield sufficient nicotine and less of less tar and gases. However, by the end of the '70s prohibitionist policies in the USA were setting a goal for a tobacco-free America by the year 2000, and precluded any development of LHCs. The persecution of smokers began with the spurious ETS issue, and with taxes raised to predatory levels - policies that became adopted by other countries around the world.

By the mid '90s, a spate of lawsuits brought the USA industry on the brink of destruction – a situation that federal and state governments desperately wanted to avoid, lest it might create a huge black market and an intractable police problem, while curtailing important tax revenues. The situation led to a settlement in the USA, whereby the cigarette industry received partial immunity from litigation in exchange for exorbitant penalties. The settlement effectively scuttled cigarette prohibition in the USA, and made State governments the majority partners in the tobacco trade.

America was not smoke free by the year 2000 and smokers continued to number well over 1 billion worldwide. The failure of prohibitionist policies prompted the Institute of Medicine (IOM) of the National Academy of Sciences of the USA to consider again the feasibility of LHCs. In a 2001 report, the IOM arrived at the same conclusions reached by the SHP of the US National Cancer Institute twenty years before, affirming that LHCs are within technical reach, and should be “[r]etaining nicotine at pleasurable or addictive levels while reducing the more toxic components of tobacco “. It also called for government regulation of LHCs, so that their health claims can be advertised.

According to epidemiologic evidence, risk relates linearly to the amount of cigarettes smoked, whereby the evidence of reduced dose should be the foundation of LHCs regulation. Because smokers inhale until a desired dose of nicotine is attained and no more, nicotine effectively limits smoke inhalation. Thus, increasing the concentration of nicotine in smoke reduces the inhalation of other smoke component. It follows that a plausible index of dose and risk reduction is the ratio of the tar to nicotine (T/N) yields of different smokes: the lower the ratio, the lower the dose of smoke and the risk.

In the USA, proponents of traditional antismoking policies are not pleased with the IOM report, for it shows how their 25 year opposition to LHCs likely caused millions of preventable deaths and diseases. Moreover, ignoring the IOM recommendations to promote LHCs would amount to a gross dereliction of a duty to protect smokers. Indeed the IOM report implies that smokers are entitled to public health services as other are, and that a policy that insults, casts out, and neglects smokers is untenable.

Because of its prominence and official status, the IOM report also requires cigarette manufacturers to aggressively develop and produce LHCs, as their clear duty of due diligence. Not doing so, the industry could become rapidly vulnerable to successful legal challenges. As an essential self-defense, the cigarette industry will have to actively seek legislation to enable the regulation and advertising of LHCs.

A billion and more people will continue to enjoy cigarettes for many decades to come, and LHCs are the inevitable answer to their needs - an answer that legislators, public health officials, and the cigarette industry will find impossible to neglect.