TOXICITY TESTING PLAN FOR LOW IGNITION-POTENTIAL CIGARETTES

U.S. Consumer Product Safety Commission and its
Expert Panel, in consultation with the
U.S. Department of Health and Human Services

20 Oct 1992 Draft

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Dear Technical Advisory Group Member:

This draft report, "Toxicity Testing Plan for Low-Ignition-Potential Cigarettes," is submitted for your review. It is also available on hard copy, floppy disk (WordPerfect), and by modem transfer.

Your input concerning research needs related to assessing the changes in health effects of these cigarettes is particularly requested. Chapter G (to be drafted) is intended for the identification and guidance on these needs.

Please refer to the chapter and page number for any specific comments you may have on the draft. (The pages of the final report will be sequentially numbered.) You may send your comments by floppy disk, modem transfer, hard copy, or fax. Please transmit your comments by 27 Nov 1992. If you have any questions or items you wish to discuss, you are welcome to contact me or my associate, Dr. Lakshmi Mishra.

Sincerely,

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HEALTH EFFECTS ASSESSMENT PLAN

I. Introduction

The Fire-Safe Cigarette Act of 1990 requires the U.S. Consumer Product Safety Commission (CPSC), in consultation with the Secretary of the U.S. Department of Health and Human Services (DHHS), to develop information on changes in the toxicity of smoke and resultant health effects of cigarettes with a reduced ability to start fires. The Act stated that CPSC "shall not obligate more than $50,000 to develop such information." The Technical Advisory Group (TAG) established by the Act agreed that this amount precluded any significant testing of prototypes. The Act succeeds the Cigarette Safety Act of 1984 which established a Technical Study Group to examine the feasibility of developing cigarettes with lowered ignition potential. The Technical Study Group concluded it is technically feasible and may be commercially feasible to develop cigarettes that will have a significantly reduced propensity to ignite upholstered furniture or mattresses.

The Act expresses a consideration for the possible nationwide health implications of changes resulting from the market substitution/entrance of low-ignition cigarette types. There were about 50 million smokers in the U.S. in 1991, according to the National Cancer Institute. The primary concern is that a small increase in the risk of a serious health effect, due to a new cigarette type, could result in a great increase in human mortality and morbidity.

CPSC staff, in consultation with DHHS and with the concurrence of the TAG, decided that in view of the statutory $50,000 limitation, a plan must be developed for the toxicological work needed. CPSC convened an expert panel to assist in the development of the plan. The panel was composed of knowledgeable scientists in the field of cigarette toxicity testing. These members were nominated by TAG members and selected by the CPSC staff.

This report discusses significant issues and recommends testing necessary for the comprehensive assessment of health effects of low-ignition potential cigarette smoke. It is not intended to be a detailed manual of cigarette toxicity testing, although some necessary technical information are presented.

II. General Discussion

Several adverse health effects of serious concern are the basis for considering the various existing toxicity tests. These effects include: lung and throat cancer, chronic obstructive lung disease, heart and vessel disease, male and female reproductive effects, fetal growth retardation, and psychophysiological addiction, as indicated in Chapter A. Not all of these health effects can be addressed at this time due to the impracticality or non-existence of adequate tests, expenses, or time lengths. Therefore, only the tests believed to be practical are recommended. Estimates of costs and time lengths for testing are included in Chapters B-F.

Major issues surrounding the testing include sidestream smoke, bases of comparisons, analytical vs. in vitro vs. in vivo testing, machine reflection of human smoking behavior, design or performance-based testing, screening paradigms, and disclosure of new additives or increased levels of existing additives, as discussed in Chapter A. Since low ignition-potential cigarettes might cause changes in smoking behaviors and therefore modify the toxicity, altered human behavior may become a significant factor in exposure, as discussed in Chapter C. Since the smoke is collected by mechanically smoking the cigarettes, the apparatus should be set to reflect smoking behavior as closely as technically feasible.

Two methods presently exist for the mechanical smoking of cigarettes, as noted in Chapter B. The Federal Trade Commission (FTC) method, established in 1969, is used in the United States, and the CORESTA method (ISO 3308-1991) is mainly used in Europe. The FTC method is described in Chapter B and is very similar to the CORESTA method. Both methods analyze for tar, nicotine, carbon monoxide, and moisture content.

In light of present knowledge on the adverse health effects and toxic constituents of cigarette smoke, further testing beyond the Federally mandated requirements for tar, nicotine, and carbon monoxide levels is needed to evaluate the toxicity. Levels of key chemical constituents known to be associated with adverse health effects need to be measured, as described in Chapter D. Cigarette smoke is a complex mixture of more than 3,500 chemicals containing at least 35 known carcinogens, and analysis of a limited number of individual chemicals may not predict the net toxic effects of the smoke. In order to address certain conglomerative toxicities of the non-gaseous constituents, in vitro and animal testing is needed, as described in Chapters E and F. Limited whole-animal testing is necessary because of the complexity of the biological systems and a variety of toxic reactions caused by cigarette smoke. As an example, pulmonary inflammation testing requires intact immune, respiratory, and cirulatory systems tc be simultaneously present.

Various data gaps exist in areas such as practical test design for reproductive effects. Chapter G identifies some of the areas and proposes research activities in support of data collection and toxicity interpretation.

The CPSC staff recommends the following guidance plan after reviewing the considerations of its expert panel and DHHS:

III. Assessment Plan

This plan provides guidance for the development of data needed to evaluate the changes in toxicity associated with low ignition-potential cigarettes. Performance-based, rather than design-based, testing will be used to provide data specific to cigarette prototypes. A screening paradigm that requires acceptable performance levels by a candidate cigarette type at one tier of tests before proceeding with the next tier is recommended. This would allow early rejection of candidates evaluated as unacceptable. However, definition of acceptable levels of performance is beyond the scope of this plan and the direction given by the Act. Therefore, the tests are presented in a sequence of tiers for screening without ascribing acceptable levels of performance at each tier.

Results of the recommended testing will be used to assess the relative toxicity of low-ignition potential cigarettes. The toxicity of a candidate low ignition cigarette should be compared to:

1) the specific marketed brand/type intended for replacement, or comparable marketed brands/types for a non-replacement candidate, and
2) standard reference cigarettes, such as the University of Kentucky standard cigarettes mentioned in Chapter E, for quality control.

There are insufficient test methods and data on exposure to cigarette smoke and resultant effects for the direct translation of the results into absolute risks to humans. Since the overall health goal is to avoid the production of greater or perhaps new toxicities than that caused by existing cigarettes, a comparative approach of assessing toxicity is appropriate.

Selection of the guidance plan tests assumes that no new additives would be present in the candidate cigarettes and that presently used additives would not exceed the levels in the current cigarettes. Since toxic effects not considered by this guidance plan could also occur, it is recommended that additives exceeding the current maximum levels of use on a per unit weight of tobacco basis must be disclosed to the U.S. Department of Health and Human Services. Confidential business information status may be requested for the data disclosed.

A. Smoking machine

The FTC method described in Chapter B is the basis for the mechanical generation of smoke constituents. Puff volume, frequency, and draw velocity may be modified as dictated by behavioral data developed from human testing (Tier III), as described in Chapter C. Unless consistent correlation of testing results of mainstream and sidestream smokes can be shown, both must be separately collected and tested.

B. Description of Tiers

An outline of four tiers is presented in Table 1. A description of the tiers follows.

Tier I - Analyses of chemicals

All constituents will be reported as per unit weight of tobacco burned, per cigarette, and per unit weight of nicotine. Moisture, nicotine, tar, and carbon monoxide will be measured according to the FTC method, as described in Chapter B. Nitric oxide will also be measured using the detector attachment to the smoking machine. The gaseous phase will be analyzed for acidity, reduction/oxidation potential, hydrogen cyanide, volatile hydrocarbons, aldehydes, and volatile nitrosamines, as described in Chapter D. The tar will be analyzed for phenols, catechols, polyaromatic hydrocarbons, and tobacco-specific nitrosamines (Chapter D).

Tier II - In vitro tests

The tar will be assayed for mutagenic activity with Ames' Salmonella test with strains TA98, 100, and 1535. The tar will also be assayed for malignant cell transforming activity, using C3H/10T1/2 mouse embryo fibroblast cells. Both mutagenicity and cell transformation assays are described in Chapter E.

Tier III - Human smoking behavior

Humans are typically the last experimental tier in testing products with potential human health effects. An example is the premarket testing of new drugs. Limited human testing to collect topographical data may proceed at this stage since the evaluation of results from Tiers I and II provide safety well beyond the presently existing FTC protocol. Additionally, the testing is limited to a couple of weeks of exposure.

Smoking behavior, including puff volume, frequency, and draw velocity of a selected group of human volunteers would be monitored, as outlined in Chapter C. Carbon monoxide (breath or blood) and cotinine (urinary, salivary, or blood) will serve as

biological markers of exposure to the smoke. If the smoking behavior data is significantly different from the FTC smoking machine settings such that an increase in exposure to the analyzed chemicals might result, then the machine must be set to reflect these data before generating smoke constituents for further Tier I and II testing and then animal testing.

Tier IV - Animal tests

Inflammatory lung response to cigarette smoke in C57Bl mice will be assayed as described in Chapter E. Tumor formation in the upper respiratory tract of random-bred golden Syrian hamsters from inhalation exposure and the skin, lungs, and other tissues of Swiss albino Ha/ICR/Mil strain mice from skin painting exposure will be examined. These two carcinogenicity tests are described in Chapter F.

All testing must conform to good laboratory practices, humane laboratory animal methods, and informed human consent procedures accepted within the scientific community. Evaluations of toxicity must be conducted by scientists possessing appropriate toxicological qualifications.

Table 1
Health Effects Assessment Plan
Outline of Tiers

Tier I - Analyses of chemicals
- Whole smoke
  - acidity
  - reduction/oxidation potential
- Gas phase
  - gases
    - carbon monoxide
    - hydrogen cyanide
    - nitric oxide
  - aldehydes
    - acetaldehyde
    - acrolein
    - proprionaldehyde
  - volatile hydrocarbons
    - benzene
    - toluene
    - 1,3-butadiene
    - isoprene
  - volatile nitrosamines
    - N-nitrosodiethylamine
    - N-nitorosdimethylamine
    - N-nitrosopyrrolidine
- Particulate phase
  - catechol
  - nicotine
  - phenols, as phenol
  - polyaromatic hydrocarbon
    - benzo(a)pyrene
  - tar-FTC
  - tobacco specific nitrosamines
    - N'-nitrosonornicotine
    - 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

Tier II- In Vitro Tests
- Salmonella mutagenicity (Ames' assay)
- mouse embryo fibroblast cell transformation assay

Tier III - Human Smoking Behavior
- cotinine
- carbon monoxide
- topography

Tier IV - Animal Tests
- mouse inflammatory lung response
- hamster upper respiratory tract carcinogenicity
- mouse skin painting carcinogenicity