Calculated Cancer Risks for Conventional and "Potentially Reduced Exposure Product" Cigarettes

James F. Pankow,[1,2] Karen H. Watanabe,[1] Patricia L. Toccalino,[1] Wentai Luo,[1] and Donald F. Austin[2,3]

[1]Department of Environmental and Biomolecular Systems, Oregon Graduate Institute School of Science and Engineering; [2]OHSU Cancer Institute; and [3]Department of Public Health and Preventive Medicine, Oregon Health and Science University, Portland, Oregon

Abstract

Toxicant deliveries (by machine smoking) are compiled and associated cancer risks are calculated for 13 carcinogens from 26 brands of conventional cigarettes categorized as "regular" (R), "light" (Lt), or "ultralight" (ULt), and for a reference cigarette. Eight "potentially reduced exposure product" (PREP) cigarettes are also considered. Because agency-to-agency differences exist in the cancer slope factor (CSF) values adopted for some carcinogens, two CSF sets were used in the calculations: set I [U.S. Environmental Protection Agency (EPA)−accepted values plus California EPA−accepted values as needed to fill data gaps] and set II (vice versa). The potential effects of human smoking patterns on cigarette deliveries are considered. Acetaldehyde, 1,3-butadiene, and acrylonitrile are associated with the largest calculated cancer risks for all 26 brands of conventional cigarettes. The calculated risks are proportional to the smoking dose z (pack-years). Using CSF set I and z = 1 pack-year (7,300 cigarettes), the calculated brand-average incremental lifetime cancer risk $\overline{\text{ILCR}}_1^{\text{acetaldehyde}}$ values are R, 6×10^{-5}; Lt, 5×10^{-5}; and ULt, 3×10^{-5} (cf. typical U.S. EPA risk benchmark of 10^{-6}). These values are similar, especially given the tendency of smokers to "compensate" when smoking Lt and ULt cigarettes. $\overline{\text{ILCR}}_1^{\text{sub}\Sigma-\text{lung}}$ is the brand-average per pack-year subtotal risk for the measured human lung carcinogens. Using CSF set I, the $\overline{\text{ILCR}}_1^{\text{sub}\Sigma-\text{lung}}$ values for R, Lt, and ULt cigarettes account for ≤2% of epidemiologically observed values of the all-smoker population average per pack-year risk of lung cancer from conventional cigarettes. R_{PREP} (%) is a science-based estimate of the possible reduction in lung cancer risk provided by a particular PREP as compared with conventional cigarettes. Using CSF set I, all R_{PREP} values are <2%. The current inability to account for the observed health risks of smoking based on existing data indicates that current expressed/implied marketing promises of reduced harm from PREPs are unverified: there is little reason to be confident that total removal of the currently measured human lung carcinogens would reduce the incidence of lung cancer among smokers by any noticeable amount. (Cancer Epidemiol Biomarkers Prev 2007;16(3):584−92)

Introduction

The enormous health toll taken by tobacco is well documented (e.g., refs. 1, 2). For the known toxicants in tobacco smoke, predictions of the corresponding health effects, as well as the study of corresponding biomarkers, require reliable information about per-cigarette toxicant "yields" (aka "deliveries"). These yields can be expected to differ to some extent among the variety of brands that are available (3). Differences will also occur within a brand over time as caused by changes in cigarette design, additive formulations, crop characteristics, and tobacco blend. Among the important blend variables are amount and type of reconstituted tobacco sheet, essentially a tobacco paper made from stems, leaf fines, and additives. Besides brand family (e.g., Marlboro, Camel, Newport, etc.), cigarette products are distinguished by being (a) conventional in design, or a "potentially reduced exposure product" (PREP); (b) 85 or 100 mm; and (c) mentholated or nonmentholated.

Studies that report the per-cigarette smoke yields (aka deliveries) of a number of carcinogens with known cancer potencies are available (e.g., ref. 4). It is of interest to assemble relevant yield data, then use the best available methods to determine whether the risks of human cancer that can be calculated can account for the epidemiologically observed risks. Also of interest is whether there are meaningful differences in the predicted risks from (a) "regular" (R; aka full flavor) cigarettes; (b) "light" (Lt) and "ultralight" (ULt) cigarettes; and (c) new PREP cigarettes that are being designed by the industry (5). The assembled yield data will also be useful in future biomarker research.

A range of PREP marketing claims have appeared: (a) Advance: "All of the taste…Less of the toxins." (6); (b) Eclipse: "May present less risk of cancer associated with smoking" and "70% lower smoking-related mutagenicity…" (7); and (c) Omni: "The three groups of carcinogens that have been significantly reduced are polycyclic aromatic hydrocarbons (PAHs), tobacco specific nitrosamines (TSNAs) and catechols. PAHs, TSNAs, and catechols are among the most potent and dangerous substances in tobacco smoke in relation to lung cancer incidence." (8). It has been argued that marketing of PREPs is likely to have negative effects on public health, including promoting smoking among existing and new smokers and impeding cessation among existing smokers (9). If the perceptions of reduced risk are then also ultimately determined to be unfounded for any given PREP brand, the consequences associated with the availability of that brand would be doubly negative. Alternatively, if some PREP brands do offer some reduction of risk for a given number of cigarettes, it will be important to compare the magnitude of that benefit against the costs of any increase in smoking and/or decrease in cessation.

The public health concerns about PREPs are due in significant measure to the history of Lt and ULt cigarettes. Indeed, whereas such cigarettes have been marketed using

wording intended to imply that they are safer and more protective of health than R cigarettes (e.g., see ref. 10), Burns et al. (11) report that epidemiologic data do not show that Lt and ULt cigarettes offer lower levels of risk as compared with R cigarettes. A recent U.S. court ruling states that ''low tar/light cigarettes offer no clear health benefit over regular cigarettes'' (12). The absence of any measurable benefit from smoking such cigarettes is due at least in part to the fact that consumers tend to smoke these cigarettes more intensely than R cigarettes to obtain certain nicotine deliveries (13, 14).

Epidemiologic studies that retrospectively examine disease incidence data for a given population can provide the final, quantitative measures of the risks of a particular per-person toxicant dose against which all other such estimates must be compared and reconciled (15). For smoking, examples of such epidemiologic studies include those of Doll and Peto (16), Villenueve and Mao (17), Holowaty et al. (18), and Bach et al. (19). However, because many smoking-related diseases take years to develop, discerning the effects of cigarette types/designs on disease incidence by means of such studies will neither be rapid nor easy. It is therefore useful to begin to address smoking risk by application of risk assessment methods that seek to predict risk based on the time-averaged doses of the carcinogens for a given toxicant portfolio. By this means, one can seek to move toward a more predictive, toxicant-by-toxicant understanding of the links between cigarette smoking and health outcomes.

Limitations and Utility of the Risk Assessment Approach as Applied to Smoking. For a given carcinogen i, risk assessment methods seek to compute the incremental (i.e., above-baseline) lifetime cancer risk $ILCR^i$ to an individual that is associated with an assumed exposure to the carcinogen. $ILCR^i$ is a fractional quantity (e.g., 0.0002). The standard approach is to compute each $ILCR^i$ based on the chronic daily intake CDI^i (mg/kg-d) of i as averaged over some assumed lifetime (e.g., 70 years; ref. 20):

$$ILCR^i = CDI^i \times CSF^i \qquad (A)$$

where CSF^i [(mg/kg-d)$^{-1}$] is the cancer slope factor (CSF; aka ''cancer potency'') for i. To the extent that risk (i.e., chance) has no units, $ILCR^i$ may be thought of as being dimensionless. (Note that the units of CDI^i and CSF^i are designed to ''cancel.'')

Any given sample of tobacco smoke is a very complex mixture. When there is simultaneous exposure to a *specific known set* of carcinogens (and especially when the carcinogens share the same mode of action), prediction of the total risk has often proceeded by a simple additivity model according to (21, 22)

$$\text{Total cancer risk} = \sum_i ILCR^i = \sum_i (CDI^i \times CSF^i) \qquad (B)$$

Unfortunately, there is limited knowledge about how multiple carcinogens actually affect organisms (e.g., the extent to which the carcinogens act independently or interact synergistically; ref. 23). In addition, in the case of tobacco smoke, irritation from the smoke can lead to increased cell proliferation and thus increased likelihood of tumor development (24). Nevertheless, at present, there is no toxicant-specific risk assessment model for complex exposures that is clearly superior to Eq. B for this application.

The total number of pack-years smoked (represented here as z) is one common measure of the total smoking exposure. (1 pack-year = 365 packs = 7,300 cigarettes.) z is the measure directly related to computation of CDI^i values. Assuming a specific lifetime (e.g., 70 years), a given carcinogen i, and constancy in the characteristics of the cigarettes smoked, then CDI^i would be proportional to z: smoking 50 pack-years will give a CDI^i that is fifty times that from 1 pack-year. By Eq. A, the cancer risk due to carcinogen i then also increases by fifty times, as does the total risk due to all carcinogens (Eq. B).

Application of Eqs. A and B to smoking assumes that variations in exposure intensity (packs/d) and duration (years of smoking) do not separately affect the risk: only their product as it appears in z is relevant. For an individual, however, it is well known that the risk of smoking-related cancer (e.g., lung cancer) is not a simple linear function of z (16, 19). Smoking-related lung cancer is thus affected not only by z but also separately by the smoking rate and the years of smoking, and indeed other variables such as age of smoking onset (16). The complexity in the dose-response relationship for smoking has motivated empirical, case-control–based searches for regression equations/models for predicting smoking risk (e.g., refs. 19, 25) and for new metrics for smoking exposure. Besides pack-years, metrics considered for lung cancer include (pack-years)$^{1/2}$ and logcig-years (= [$\log_e$(cigarettes per day + 1)] × years; refs. 26, 27). The latter metric provides a way to separately consider the effects of smoking intensity and smoking duration (26, 27). However, even as there is a continuation of effort to improve the prediction of smoking risks by purely empirical means, interest remains exceedingly strong in considering the potential consequences of specific carcinogens in the smoke generated by both conventional cigarettes and PREPs (5). For that, at present, one must rely on Eqs. A and B, despite their simplistic reliance on z as the dose metric and the assumption of simple additivity. Eqs. A and B are the basis of an important check on the status of our understanding of the carcinogenicity of the smoke from conventional cigarettes, as well as the starting point for the examination of any implicit or explicit marketing claims of reduced harm from PREPs.

Prior applications of risk assessment principles to smoking risk have been reported (28, 29). Vorhees and Dodson (28) used yield data for smoke constituents from multiple brands of conventional cigarettes to calculate cancer risks due to 30 smoke carcinogens but did not include comparisons among brands within a given cigarette type or among cigarette types. Fowles and Dybing (29) surveyed multiple sources of cigarette yield data, then computed cancer risk indices for 41 smoke carcinogens (as well as health effects for 17 noncarcinogens), but solely for an estimate of the average conventional cigarette.

Here, according to the logic outlined in Table 1, we undertake calculations of cancer risks by brand and by cigarette type using averages for each of four main cigarette types of interest (R, Lt, ULt, and PREP). We also consider the results as compared with epidemiologically observed risks of lung cancer because that form of cancer is most clearly linked to smoking.

Table 1. Observations on smoking-related disease and risk assessment calculations

(a) Cigarette smoking causes considerable human disease, including many cases of lung cancer.
(b) Risk assessment methods use toxicant-by-toxicant exposure estimates to predict estimates of the incidence of cancer in humans.
(c) Cigarette yield data are available that give the per cigarette deliveries of some toxicants of interest in cigarette smoke.
(d) Risk assessment predictions of disease risk from smoking can be obtained based on available cigarette yield data for use in determining:
(i) How the risk assessment-calculated risks compare among three types of conventional cigarettes (regular, light, ultralight) and for PREPs;
(ii) How risk assessment-calculated risks for regular, light, and ultralight cigarettes comport with the observed levels of risk of smoking conventional cigarettes;
(iii) Whether the risk assessment-predicted levels of risk for PREP cigarettes are meaningfully lower than risks from conventional cigarettes.

Table 2. Nomenclature terms of importance in this work for consideration of the risk due to toxicants in tobacco smoke

Term	Meaning	Units
i	A toxicant of interest (e.g., 1,3-butadiene, benzene, N-nitrosonornicotine, NNK, etc.)	—
A^i	Per cigarette smoke delivery (aka yield of toxicant i)	µg/cigarette
z	Total smoking dose in pack-years	pack-years
CDI_1^i	Average (chronic) rate of daily intake of toxicant i by smoking when the total smoking dose is 1 pack-year and, in this work, when the dose is averaged over 70 y	mg/kg d
CDI_z^i	Average (chronic) rate of daily intake of toxicant i by smoking when the total smoking dose is z pack-years and, in this work, when the dose is averaged over 70 y	mg/kg-d
CSF^i	Cancer slope factor for carcinogen i (also known as the cancer potency of i)	$(mg/kg-d)^{-1}$*
$ILCR_1^i$	Incremental calculated lifetime cancer risk for carcinogen i for a $z = 1$ pack-year smoking dose	risk for 1 pack-year
$ILCR_z^i$	Incremental calculated lifetime cancer risk for carcinogen i for a smoking dose of z pack-years	risk for z pack-years
$\overline{ILCR_1^i}$	Average calculated value of the $ILCR_1^i$ for a given group of cigarettes of a certain type (e.g., the average for all light cigarettes)	risk for 1 pack-year
$sub\Sigma$	A subtotal for a specific subset of carcinogens	—
$sub\Sigma$-lung	A subtotal for a specific subset of human lung carcinogens	—
$ILCR_1^{sub\Sigma}$	A subtotal of individual calculated $ILCR_1^i$ for all carcinogens measured, with the smoking dose $z = 1$ pack-year	risk for 1 pack-year
$\overline{ILCR_1^{sub\Sigma}}$	Average value of calculated $ILCR_1^{sub\Sigma}$ for a given group of cigarette brands of a certain type (e.g., the average for light brands)	risk for 1 pack-year
$ILCR_1^{sub\Sigma - lung}$	SubΣ of individual calculated $ILCR_1^i$ for all human lung carcinogens that have been measured (analytically), for a $z = 1$ pack-year smoking dose	risk for 1 pack-year
$\overline{ILCR_1^{sub\Sigma - lung}}$	Average value of calculated $ILCR_1^{sub\Sigma - lung}$ for a given group of cigarette brands of a certain type (e.g., the average for light brands)	risk for 1 pack-year
$ILCR_z^{obs\Sigma - lung}$	Actual observed risk from smoking z pack-years	risk for z pack-years
M	Percent match between $\overline{ILCR_1^{sub\Sigma - lung}}$ for conventional cigarettes and Ω_1^{lung}	%
R_{PREP}	Amount by which the calculatable per pack-year risk of lung cancer is reduced by switching from conventional cigarettes to a particular PREP	%
Ω_1^{lung}	Observed total $ILCR^{\Sigma - lung}$ risk per pack-year for lung-cancer for $z = 1$ pack-year as averaged over all smokers and all smokers' doses in a particular real population (not a subΣ, but the full observed Σ)	risk per pack-year

NOTE: For each ILCR value, a specific CDI is assumed. The units of each ILCR are ''fractional risk.'' For exposed individual, an ILCR = 0.001 indicates a 1 in 1,000 chance of cancer above the background risk.
*Because a CSF is a slope of cancer incidence versus CDI, a CSF may alternately be viewed as having units of risk/(mg/kg d).

Materials and Methods

Nomenclature Considerations. Multiple terms and symbols are used in the discussion of $ILCR^i$ values for individual carcinogens i as a function of the smoking dose z (e.g., 1 pack-year, 5 pack-years, etc.). For example, in consideration of Eq. B, when summing the risks from multiple carcinogens measured in tobacco smoke, notation is required that emphasizes that any such summation is a partial sum, denoted here as subΣ. (The enormous complexity of tobacco smoke means that it is likely that it will never be possible to know the levels and cancer potencies of all of the individual carcinogens in any sample of tobacco smoke.) Table 2 summarizes the terms that provide the focus of the final discussion; the definitions of other terms and abbreviations are given only where first introduced.

Effects of Machine versus Human Smoking on Cigarette Yield (Delivery) Values. Numerous smoker-to-smoker differences exist in the smoking process, and indeed from day to day for a given smoker. The differences are both idiosyncratic and stochastic in nature, and even a given smoker is subject to idiosyncratic differences because smoking habits tend to evolve with the passage of time. As a result, there is no single ''human smoking condition,'' and both ''smoking topography'' and degree of vent-hole blocking can vary widely. (''Smoking topography'' = smoke flow rate versus time.) For particular cigarettes of interest, efforts to obtain cigarette yield data under human smoking conditions can therefore only capture yield information applicable to the subject smokers for the days (and hours of the day) of the testing.

Given the logistical difficulties, nonuniformities, and uncertainties associated with cigarette yield data obtained under human smoking conditions, considerably more cigarette yield data have been acquired using standardized machine smoking protocols than using human-derived smoking conditions. The yield values used here were obtained by machine smoking, mostly by the Massachusetts (MA) protocol. The possible magnitudes of typical differences caused by human smoking patterns versus standard machine smoking protocols may be considered as follows.

Yield values can be expected to depend primarily on the total smoke volume $V_{s,tot}$ (mL, per cigarette), although variation in puff size over the course of the cigarette (e.g., constant puff size throughout versus larger initial puffs followed by smaller puffs) can also play a role. The Federal Trade Commission (FTC) machine smoking protocol (30) is characterized as (*a*) sequential 35-mL, 2-s puffs every 60 s; (*b*) no blocking of filter ventilation holes; and (*c*) smoking to a ''butt length'' equal to either the filter overwrap (''tipping'') paper + 3 mm, or the filter length + 8 mm, whichever is greater (although in any case not less than 23 mm). The number of puffs per cigarette varies by brand, moisture content, etc., but ~8 puffs is typical, giving $\hat{V}_{s,tot}^{FTC} \approx 280$mL.

In a review of human puffing patterns (31) with conventional cigarettes, the average puff volume is 43 mL and the average number of puffs is 11, suggesting $V_{s,tot} \approx 470$ mL. In a study with 133 smokers, Djordjevic et al. (3) observed an average $V_{s,tot}$ value of ~550 mL for R cigarettes, and ~640 mL for ''low nicotine'' cigarettes (Lt, etc.); Lee et al. (32) measured $V_{s,tot} \approx 630$ mL for human subjects smoking their own brand. These human $V_{s,tot}$ values are roughly $2 \times V_{s,tot}^{FTC}$.

The MA machine-smoking protocol was developed to address the view that cigarettes are typically smoked more intensely than described by the FTC protocol. The MA protocol (4) is (*a*) 50% blocking of filter ventilation holes; (*b*) sequential 45-mL, 2-s puffs every 30 s; and (*c*) the same butt length criterion as in the FTC protocol. As with the FTC protocol, the number of puffs per cigarette varies, but ~9 puffs is typical, giving $V_{s,tot}^{MA} \approx 405$mL and a MA/FTC smoke volume ratio of ~1.5. In a comparison of yield values obtained by the MA and FTC protocols, an overall average MA/FTC yield ratio of ~2 for the brands and analytes considered has been obtained (33). This is consistent with the MA/FTC smoke volume ratio,

particularly when the use of 50% vent hole blocking by the MA protocol is considered.

Detailed studies have not been carried out on the effect of variable puff size on yield values for the range of toxicants of interest here. In the absence of such information, according to the above observations for the FTC and MA protocols [in particular, the results of Roemer et al. (33)], $V_{s,tot}$ was judged to be a reasonable first-approximation scaling factor for yield values for different smoking topographies, including human topographies. Considering the results of Djordjevic et al. (3) and Lee et al. (32) discussed above, typical human $V_{s,tot}$ values might be approximated as $\sim 1.5 V_{s,tot}^{MA}$, so that toxicant yield values for human topographies with a given type of conventional cigarette (R, Lt, ULt) are not likely to be systematically larger by more than $2\times$ when compared with yield values obtained by the MA protocol.

Given that PREPs are designed with the general intent of reducing constituents that are characteristic of tobacco smoke, human smoking of such products may tend to be significantly more intense than with conventional cigarettes: observations of human smoking of the Eclipse PREP gave $V_{s,tot} \approx 1,350$ mL (32). According to this view, yield values obtained for PREPs by machine smoking with $V_{s,tot} = 300$ to 400 mL may require upward adjustment by more than $2\times$, which would tend to increase the calculated toxicity of PREPs.

CDI and Smoking Dose z. In an elaboration of the general approach taken by others (28, 29), for any given toxicant i of interest, straightforward application of risk assessment methods (20) leads to

$$CDI^i \text{ (mg/kg-d)} = \frac{A^i \times 10^{-3} \text{ mg/}\mu\text{g} \times \overline{SR} \times 365 \text{ days/y} \times ED}{BW \times AT}$$

(C)

where CDI^i (mg/kg-d) and A^i (μg/cigarette) are defined in Table 2; $\overline{SR}$ (cigarettes/d), average smoking rate; ED (years), exposure (smoking) duration; BW (kg), body weight; and AT (days), averaging time for the smoking dose. Following others (28, 29), Eq. C uses the assumption that 100% of the toxicant is deposited in the respiratory tract, as would be typical for any conservative risk assessment calculation.

A given smoking dose z (pack-years) can be achieved in any number of ways. For $z = 1$ pack-year, one pack (20 cigarettes) can be smoked per day for 1 year, or 1 cigarette can be smoked per day for 20 years. The total quantity of cigarettes smoked is given by $\overline{SR} \times 365$ days/y $\times$ ED. Thus,

$$z = \frac{\overline{SR} \times 365 \text{ days/y} \times ED}{7,300 \text{ cigarettes/pack} - \text{year}}$$

(D)

Substitution into Eq. A gives as a function of z:

$$CDI_z^i \text{ (mg/kg-d)} = \frac{A^i \times 10^{-3} \text{ mg/}\mu\text{g} \times z \times 7,300}{BW \times AT}$$

(E)

so that, when $z = 1$ pack-year

$$CDI_1^i \text{ (mg/kg-d)} = \frac{A^i \times 10^{-3} \text{ mg/}\mu\text{g} \times 7,300}{BW \times AT}$$

(F)

ILCR Values. For carcinogen i, the ILCR for a smoking dose $z = 1$ pack-year is calculated according to

$$ILCR_1^i = CDI_1^i \times CSF^i$$

(G)

As a function of z, we have

$$ILCR_z^i = CDI_z^i \times CSF^i$$

(H)

where CSF^i is the CSF (cancer potency) for carcinogen i with units commonly given as (mg/kg-d)$^{-1}$, or, more precisely, risk/(mg/kg d); see Table 2.

By Eq. E, CDI_z^i scales linearly with z according to

$$CDI_z^i = z\, CDI_1^i$$

(I)

Thus, in this linear risk model, by Eqs. G, H, and I, the risk also scales linearly with z:

$$ILCR_z^i = z\, ILCR_1^i$$

(J)

Whereas a linear risk model as embodied in Eq. J is a standard approach in estimations of risk, it is important to reemphasize that the available epidemiologic evidence (e.g., refs. 16, 19, 26, 27) suggests that a linear, z-only model does not exactly apply to smoking related disease. This matter is addressed further below.

SubΣ Cancer Risks (ILCR$^{sub\Sigma}$). In a specific application of Eq. B, for human lung carcinogens, we define

$$ILCR_1^{sub\Sigma - lung} = \sum_{lung\ carcinogens} ILCR_1^i$$

(K)

where the right hand side is the sum over all human lung carcinogens for which cigarette yield and CSF data are available (in this work, formaldehyde, acrylonitrile, arsenic, and cadmium).

As noted above, the use of subΣ emphasizes that any attempt to sum ILCR values for tobacco smoke will yield a subtotal of the risk terms, not the full total. Nevertheless, the determined study of the composition and toxicology of tobacco smoke (including mixture, nonlinear, cancer-promoter, and irritation effects) may eventually allow predicted values of ILCR$_z^{sub\Sigma - lung}$ (including for $z = 1$) to approach the corresponding observed total lung-cancer risk sum for z. When averaged over all smoking doses, the observed population average risk per pack-year is discussed below as Ω_1^{lung}.

In a second application of Eq. B, we define the subΣ for all carcinogens for which cigarette yield and toxicity data are available, regardless of cancer end point or animal model. For example, 4-(N'-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and benzo[a]pyrene are known rodent lung carcinogens. Therefore,

$$ILCR_1^{sub\Sigma} = \sum_i ILCR_1^i$$

(L)

where $\Sigma_i ILCR_1^i$ is the sum over all carcinogens for which cigarette yield and CSF data are available (in this work, 13 carcinogens). Analogues of Eq. J can be written for Eq. K and for Eq. L.

Cigarette Yield (Delivery) Data. Supplementary Table S1A to D contains the cigarette yield data considered here. The data pertain to multiple toxicants for each of 26 brands of conventional commercial cigarettes, one conventional reference cigarette (the 1R4F, a Lt cigarette), four PREP prototypes, and four PREP versions that have been commercially marketed. For the 26 R, Lt, and ULt brands and the 1R4F, all data were obtained from the 1999 Massachusetts Benchmark Study (4), which reported average yield values (five replicates)

for 41 smoke constituents, plus tar, carbon monoxide, and nicotine. Only the carcinogen data are used here.

The Massachusetts Benchmark Study (4) used the MA machine-smoking protocol (see above). The cigarettes were categorized here according to tar yields that have been reported (30) using the FTC smoking protocol. In this work, three bins by tar yield are defined: (a) R, ≥ 15 mg; (b) Lt, 6 to <15 mg; and (c) ULt, 1 to <6 mg. (Whereas the descriptor "medium" has also been used with commercial conventional cigarettes, three bins were considered adequate.) The bin assignments made here do not in all cases equate with the designations used by the manufacturers. The data for the 1R4F were excluded when calculating means and SDs for ILCR values for the Lt category.

Some PREP cigarette yield data are available (6, 34-43), including data found in several once-secret tobacco industry documents (40-43). The PREP yield data used here were obtained as follows: TOB-HT prototype (34); "electrically heated cigarette" prototype (35); XDU 2-104 prototype (40); XDU 740 prototype (40); Premier (40); Advance "Light" Kings and "Light" 100s (6); and Eclipse (36). Only various subsets of the toxicants measured for the conventional cigarettes considered were measured for the PREPs in the studies considered. In addition, a number of the PREP studies contained only incomplete information on (a) the number of samples/replicates and (b) the smoking protocol used [e.g., Borgerding et al. (40) do not provide details on the smoking protocol used for the Premier and XDU prototypes]. No adjustments to the PREP yields were made here to compensate for such differences in smoking protocol: doing so would not have been straightforward given the incomplete method descriptions found in some of those studies, and, moreover, not likely to introduce much more than a factor of 2 change in the results (see above discussion of effects of smoking topographies).

Values of Body Weight, Averaging Time, and CSF^i. Following U.S. EPA (20), for body weight and averaging time, the default values of 70 kg and 70 years × 365 days/y were adopted. ILCR values were calculated using two sets of the CSF^i. For set I (see Table 3), values were obtained from the U.S. EPA Integrated Risk Information System data base (44) where available, and if gaps existed in the Integrated Risk Information System database, by using values from the California EPA Office of Environmental Health Hazard Assessment (45, 46). For set II (see Table 4), the converse process was used. The California EPA CSF^i values for 1,3-butadiene, acrylonitrile, benzene, and cadmium are 5.5, 4.2, 3.7, and 2.4 times higher, respectively, than the corresponding U.S. EPA values.

For two carcinogens, quinoline and the tobacco-specific nitrosamine NNK, it was necessary to use CSF values based on p.o. administration (45, 47). CSF^i values for 11 other carcinogens were obtained by conversion of tabulated values of the inhalation unit risk [IUR^i, $(\mu g/m^3)^{-1}$]. Following U.S. EPA (20), those conversions assumed BW = 70 kg and average daily inhalation rate (IR) = 20 m^3/d:

$$\text{CSF}^i \ (\text{mg/kg-d})^{-1} = \frac{\text{IUR}^i \ (\mu g/m^3)^{-1} \times \text{BW (kg)}}{\text{IR} \ (m^3/d) \times 10^{-3} \ (\text{mg}/\mu g)} \quad \text{(M)}$$

Results

For the carcinogens considered here, values of ILCR$_1^i$ averaged over brand within a cigarette type are denoted $\overline{\text{ILCR}}_1^i$ and given in Table 3 as based on CSF set I and in Table 4 as based CSF set II. Corresponding values of $\overline{\text{ILCR}}_z^i$ for other values of z can be obtained by proportion (see Eq. J). The brand-dependent $\overline{\text{ILCR}}_1^i$ values that underlie the $\overline{\text{ILCR}}_1^i$ values are summarized in Supplementary Table S2A to D for CSF set I and in Supplementary Table S3A to D for CSF set II. Supplementary Figs. S1 to S4 provide a comparison of the $\overline{\text{ILCR}}_1^i$ obtained here with average $\overline{\text{ILCR}}_1^i$ for conventional cigarettes derived from Voorhees and Dodson (28) for (a) cigarette yield data in the 1989 Surgeon General's report (48)

Table 3. Summary statistics [mean $(\overline{\text{ILCR}}_1^i)$ and SD] based on CSF set I by cigarette type for ILCR values for 13 carcinogens for $z = 1$ pack-year

Toxicant	CASRN	CSF set I $(\text{mg/kg-d})^{-1}$	R $\overline{\text{ILCR}}_1^i$	R SD	Lt $\overline{\text{ILCR}}_1^i$	Lt SD	ULt $\overline{\text{ILCR}}_1^i$	ULt SD	PREP $\overline{\text{ILCR}}_1^i$	PREP SD
Acetaldehyde	75-07-0	0.0077*	6e−05	6e−06	5e−05	6e−06	3e−05	1e−05	4e−06	4e−06
Acrylonitrile	107-13-1	0.24*	3e−05	6e−06	3e−05	8e−06	2e−05	7e−06	4e−06	3e−06
4-Aminobiphenyl	92-67-1	21[†]	5e−07	9e−08	4e−07	4e−08	2e−07	6e−08	2e−07	9e−08
Arsenic	7440-38-2	15*	9e−07	3e−07	7e−07	2e−07	4e−07	2e−07	2e−08	NA[‡]
Benzene	71-43-2	0.027*	9e−06	1e−06	9e−06	1e−06	6e−06	2e−06	1e−06	1e−06
Benzo[a]pyrene	50-32-8	3.9[†]	5e−07	8e−08	4e−07	5e−08	2e−07	6e−08	4e−08	5e−08
1,3-Butadiene	106-99-0	0.11*	4e−05	7e−06	4e−05	8e−06	2e−05	8e−06	5e−06	5e−06
Cadmium	7440-43-9	6.3*	5e−06	7e−07	3e−06	6e−07	2e−06	7e−07	3e−07	2e−07
Formaldehyde	50-00-0	0.046*	2e−05	3e−06	1e−05	4e−06	5e−06	2e−06	2e−06	2e−06
Lead	7439-92-1	0.042[†]	1e−08	2e−09	1e−08	2e−09	5e−09	2e−09	3e−09	1e−10
NNK[§]	64091-91-4	49[‖]	4e−05	5e−06	3e−05	5e−06	2e−05	6e−06	4e−06	7e−07
N-Nitrosonornicotine	80508-23-2	1.4[†]	2e−06	3e−07	1e−06	3e−07	8e−07	3e−07	1e−07	6e−08
Quinoline[§]	91-22-5	3*	2e−05	8e−06	1e−05	4e−06	7e−06	2e−06	2e−06	1e−06
Cancer risk subtotals										
Human lung carcinogens*,[¶] ILCR$_1^{\text{sub}\Sigma-\text{lung}}$			5e−05	1e−05	4e−05	1e−05	2e−05	9e−06	4e−06	5e−06
All cancers: ILCR$_1^{\text{sub}\Sigma}$			2e−04	2e−05	2e−04	3e−05	1e−04	3e−05	2e−05	2e−05

NOTE: Conventional cigarettes classified by FTC tar yield as follows (30): regular, tar ≥ 15.0 mg; light, 6.0 mg $\leq$ tar < 15.0 mg; and ultralight, 1.0 $\leq$ tar < 6.0 mg. PREP cigarettes not characterized by tar content.
Abbreviation: CASRN, Chemical Abstracts Registry Number.
*Integrated Risk Information System, U.S. Environmental Protection Agency (44).
[†] Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Sept. 2004 Cancer Potency List (46).
[‡] NA, not available; limited PREP yield data did not allow calculations for some chemicals. The mean $(\overline{\text{ILCR}}_1^i)$ for each chemical corresponds to a different number of PREPs because each PREP study measured different chemicals.
[§] CSF was determined from an oral exposure study.
[‖] CSF, 49 for all cancer end points. California Environmental Protection Agency. Sept. 2001 Expedited Cancer Potency Values and No Significant Risk Levels for Six Proposition 65 Carcinogens (47).
[¶] $\overline{\text{ILCR}}_1^{\text{sub}\Sigma-\text{lung}}$ = sum of $\overline{\text{ILCR}}_1^i$ for known human lung carcinogens considered here: acrylonitrile, arsenic, cadmium, and formaldehyde.

Table 4. Summary statistics (mean ($\overline{ILCR}_1^i$) and SD) based on CSF set II by cigarette type for ILCR values for 13 carcinogens for $z = 1$ pack-year

Toxicant	CASRN	CSF set II $(mg/kg-d)^{-1}$	R		Lt		Ult		PREP	
			$\overline{ILCR}_1^i$	SD	$\overline{ILCR}_1^i$	SD	$\overline{ILCR}_1^i$	SD	$\overline{ILCR}_1^i$	SD
Acetaldehyde	75-07-0	0.01*	7e−05	8e−06	7e−05	8e−06	4e−05	1e−05	5e−06	5e−06
Acrylonitrile	107-13-1	1.0*	1e−04	3e−05	1e−04	3e−05	6e−05	3e−05	1e−05	1e−05
4-Aminobiphenyl	92-67-1	21*	5e−07	9e−08	4e−07	4e−08	2e−07	6e−08	2e−07	9e−08
Arsenic	7440-38-2	12*	8e−07	2e−07	6e−07	2e−07	3e−07	2e−07	2e−08	NA[†]
Benzene	71-43-2	0.1*	4e−05	5e−06	3e−05	4e−06	2e−05	8e−06	4e−06	4e−06
Benzo[a]pyrene	50-32-8	3.9*	5e−07	8e−08	4e−07	5e−08	2e−07	6e−08	4e−08	5e−08
1,3-Butadiene	106-99-0	0.6*	2e−04	4e−05	2e−04	4e−05	1e−04	4e−05	3e−05	3e−05
Cadmium	7440-43-9	15*	1e−05	2e−06	8e−06	1e−06	4e−06	2e−06	6e−07	5e−07
Formaldehyde	50-00-0	0.021*	7e−06	1e−06	5e−06	2e−06	2e−06	1e−06	1e−06	1e−06
Lead[‡]	7439-92-1	0.042*	1e−08	2e−09	1e−08	2e−09	5e−09	2e−09	3e−09	1e−10
NNK	64091-91-4	49[§]	4e−05	5e−06	3e−05	5e−06	2e−05	6e−06	4e−06	7e−07
N-Nitrosonornicotine	80508-23-2	1.4*	2e−06	3e−07	1e−06	3e−07	8e−07	3e−07	1e−07	6e−08
Quinoline[‡]	91-22-5	3[‖]	2e−05	8e−06	1e−05	4e−06	7e−06	2e−06	2e−06	1e−06
Cancer risk subtotals										
Human lung carcinogens[‖,¶] $\overline{ILCR}_1^{sub\Sigma-lung}$			1e−04	3e−05	1e−04	3e−05	7e−05	3e−05	1e−05	1e−05
All cancers: $\overline{ILCR}_1^{sub\Sigma}$			5e−04	7e−05	5e−04	8e−05	3e−04	9e−05	4e−05	5e−05

NOTE: Conventional cigarettes classified by FTC tar yield as follows (30): regular, tar ≥ 15.0 mg; light, 6.0 mg ≤ tar < 15.0 mg; and ultralight, 1.0 ≤ tar < 6.0 mg. PREP cigarettes not characterized by tar content.
*Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Sept. 2004 Cancer Potency List (46).
[†]NA = not available: limited PREP yield data did not allow calculations for some chemicals. Each mean corresponds to a different number of PREPs because each PREP study measured different chemicals.
[‡]CSF was determined from an oral exposure study.
[§]CSF, 49 for all cancer end points. California Environmental Protection Agency. Sept. 2001 Expedited Cancer Potency Values and No Significant Risk Levels for Six Proposition 65 Carcinogens (47).
[‖]Integrated Risk Information System, U.S. Environmental Protection Agency (44).
[¶]$\overline{ILCR}_1^{sub\Sigma-lung}$ = sum of $\overline{ILCR}_1^i$ for known human lung carcinogens considered here: acrylonitrile, arsenic, cadmium, and formaldehyde.

and (b) 1999 yield data for cigarettes marketed by Imperial Tobacco (49) in British Columbia. The $\overline{ILCR}_1^i$ obtained here using CSF set II are generally similar to the values derived from Voorhees and Dodson (28) for Imperial Tobacco cigarettes smoked according to an "intense" machine smoking protocol.

Based on CSF set I, for 24 of the 26 commercial brands of conventional cigarettes and for the 1R4F, the rank order of the carcinogens for the three highest values is the same: acetaldehyde ≥ 1,3-butadiene ≥ NNK. The two exceptions are Marlboro King filtered Lt soft pack (acetaldehyde > acrylonitrile > 1,3-butadiene = NNK) and Now King filtered soft pack (acetaldehyde > 1,3-butadiene = acrylonitrile). Based on CSF set II, the rank order for the carcinogens with the three highest is the same for all 26 commercial brands of conventional cigarettes and for the 1R4F (i.e., 1,3-butadiene ≥ acrylonitrile ≥ acetaldehyde). For the PREPs considered, for both CSF sets I and II, the rank order for $ILCR_1^i$ varies by PREP version. For the Eclipse and the two versions of Advance, a significant number of $ILCR_1^i$ are $\geq 10^{-6}$, which is an EPA regulatory benchmark risk for exposure to carcinogens in ambient air (50). For CSF set II, several of the $ILCR_1^i$ for the two versions of Advance are $>10^{-5}$.

For CSF set I, for all three types of conventional cigarettes, $\overline{ILCR}_1^i \geq 10^{-5}$ for acetaldehyde, acrylonitrile, and 1,3-butadiene (Table 3). For CSF set II, for all three types of conventional cigarettes, $\overline{ILCR}_1^i \geq 10^{-5}$ for acetaldehyde, acrylonitrile, benzene, 1,3-butadiene, and NNK (Table 4). Figure 1 provides a comparison of the $\overline{ILCR}_1^i$ values by cigarette type for acetaldehyde, acrylonitrile, 1,3-butadiene, and NNK. For each of these constituents, whether by CSF set I or CSF set II, R and Lt cigarettes are characterized by similar mean values. Although lower, the $\overline{ILCR}_1^i$ values for ULt and PREP cigarettes are within factors of ∼2 and ∼10 of the values for R and Lt cigarettes, respectively.

Each brand-specific value of $ILCR_1^{sub\Sigma}$ and $ILCR_1^{sub\Sigma-lung}$ for R, Lt, and ULt cigarettes is plotted in Fig. 2A to C along with the associated mean values ($\overline{ILCR}_1^{sub\Sigma}$ and $\overline{ILCR}_1^{sub\Sigma-lung}$). Two observations can be made: (a) even without invoking smoking

"compensation" effects, the $\overline{ILCR}_1^{sub\Sigma}$ values for all three types of conventional cigarettes are very similar (by CSF set I, 2×10^{-4} for both R and Lt cigarettes and 1×10^{-4} for ULt cigarettes; by CSF set II, 5×10^{-4} for both R and Lt cigarettes and 3×10^{-4} for ULt cigarettes); (b) elevation of the $\overline{ILCR}_1^{sub\Sigma}$ for ULt cigarettes by a factor of 2 is within the range of the effect of compensation on toxicant yields for ULt versus R cigarettes (e.g., refs. 13, 14). Analogous observations can be
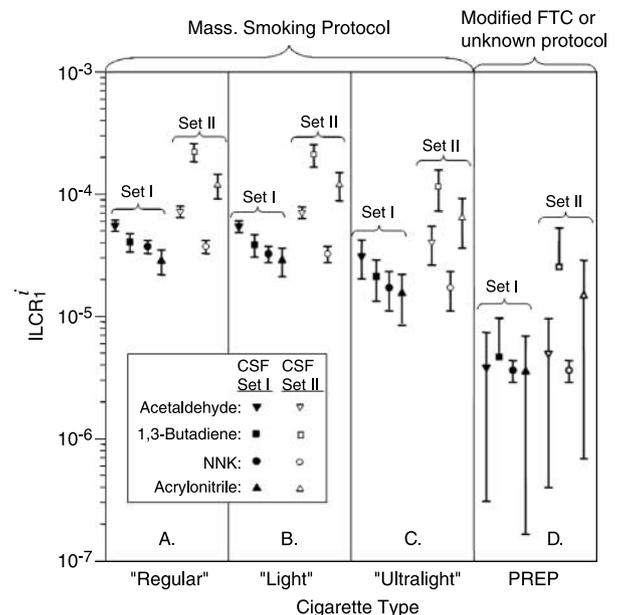

Figure 1. $ILCR_1^i$ values for the four toxicants associated with the highest calculated cancer risks from cigarettes. Markers denote $\overline{ILCR}_1^i$, which is the average across cigarettes within each type; bars denote 1, SD. For 1,3-butadiene from PREP cigarette brands, using both CSF sets I and II, the quantity $\overline{ILCR}_1^i$ − 1 SD is negative and so was not plotted.
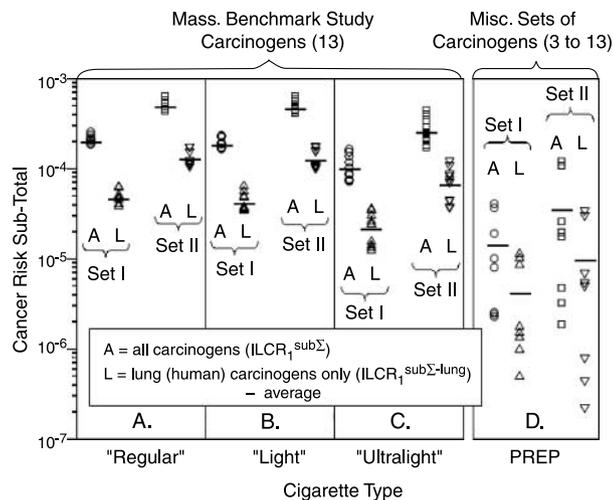
Figure 2. Brand-specific incremental lifetime cancer risk subtotals: $ILCR_1^{sub\Sigma}$ (all cancer end points) and $ILCR_1^{sub\Sigma-lung}$ (known human lung carcinogens only) for both CSF sets I and II. The average values $\overline{ILCR_1}^{sub\Sigma}$ and $\overline{ILCR_1}^{sub\Sigma-lung}$ are marked.

made for $\overline{\overline{ILCR_1}}^{sub\Sigma-lung}$. Overall, these results are consistent with the observation that, on average, Lt and ULt cigarettes are not more protective of smokers' health than R cigarettes (11).

Not all of the carcinogens measured for R, Lt, and ULt cigarettes in the Massachusetts Benchmark Study (4) were determined in the various PREP studies. The subΣ risk values presented in Fig. 2D therefore pertain to various more limited subΣ values than could be computed for the other cigarette types. Nevertheless, each of the "all carcinogen" subΣ risk values for the PREPs was found to be $>10^{-6}$, whether by CSF set I or II. Moreover, just as compensation has been observed with Lt and ULt cigarettes, PREPs may tend to be smoked more intensely than conventional cigarettes. For example, as noted, Lee et al. (32) observed total smoke volumes ($V_{s,tot}$) of ~1,350 mL for smokers with the Eclipse as compared with the ~405 mL/cigarette expected from the MA protocol. A factor of 3× increase in deliveries due to intense smoking for PREPs would bring $\overline{ILCR_1}^{sub\Sigma}$ for the PREPs to within half of that for ULt cigarettes.

Discussion

Measures of the Observed Average Lung Cancer Risk. Placing the per pack-year cancer risk values calculated here into proper context requires an understanding of the actual cancer risks indicated by available epidemiologic data. This can be undertaken most easily with lung cancer given that ~90% of male lung cancer deaths and 75% to 80% of female lung cancer deaths each year are due to smoking (48, 51).

Lifetime probabilities of lung cancer for Canadian current smokers and "never smokers" were studied by Villeneuve and Mao (17) for 1987-1988. Their results suggest that the lifetime (0-85+ years) smoking-related risk of lung cancer for "current smokers" is ~0.16 for men and ~0.11 for women. Because the current male/female ratio for lung cancer incidence rate in Canada is ~60:40 (52), these values imply an average risk of ~0.14 for all current smokers in that work. Data for 1985-1991 indicate a population in Canada for ages 15+ years of ~20,000,000 (53), a smoking prevalence of ~30% for that group (54), and thus ~6,000,000 smokers. Sales of manufactured cigarettes in Canada over the preceding decade averaged ~55 billion cigarettes per year (55). Adding in another ~16% due to a "roll your own" component (56), the result is ~64 billion cigarettes per year, or ~9,000,000 pack-years each year. This indicates an average cigarette consumption of ~1.5 pack-

year/y for all smokers (11,000 cigarettes/y); it is assumed that the smoking rate (among smokers) was roughly similar in preceding years. Assuming that a typical smoking duration is 30 to 50 years, the result is ~45 to 75 pack-years. Pankow et al.[4] denote the observed population-average per pack-year risk as Ω_1^{lung}. In a linear risk model (e.g., as with Eq. J), the risk of ~0.14 thus corresponds to a per pack-year risk of $\Omega_1^{lung} = 0.0019$ to ~0.0031. By a different method, for Canada and United States, Pankow et al.[4] obtain $\Omega_1^{lung} = 0.00241$ and 0.00243 cases/pack-year, respectively. Because Ω_1^{lung} reflects the population-average per pack-year risk as averaged over all smokers and all smoker doses, it is a relevant value against which brand-specific $ILCR_1^{sub\Sigma-lung}$ values and the cigarette-type averages $\overline{ILCR_1}^{sub\Sigma-lung}$ can be compared. It also satisfies the expectation of an overall linear relationship between risk and a population average of the smoking dose.

Percent Match between Predicted and Observed Risks. If it is assumed that the carcinogen A^i values considered here for conventional cigarettes are representative of historical A^i values for cigarettes from the preceding decades, then one can examine the degree of match between the predicted and observed risks of lung cancer. By none of the methods used below to consider this match, however, do the predicted risks come close to matching the observed risks.

First, the match M (%) between the subΣ risk for human lung carcinogens from a 1 pack-year dose of conventional (conv) cigarettes and the actual observed population-average lung cancer risk Ω_1^{lung} can be defined:

$$M\ (\%) \equiv \frac{(\overline{ILCR_1}^{sub\Sigma-lung})_{conv}}{\Omega_1^{lung}} \times 100\% \qquad (N)$$

Based on CSF set I, for R, Lt, and ULt conventional cigarettes, $\overline{ILCR_1}^{sub\Sigma-lung} = 5 \times 10^{-5}$, 4×10^{-5}, and 2×10^{-5}, respectively (Table 3). Taking $\Omega_1^{lung} \approx 0.0024$, then $M \leq 2\%$ for all three types, and thus for any mix of such conventional cigarettes as may currently be smoked. Based on CSF set II, $\overline{ILCR_1}^{sub\Sigma-lung} = 1 \times 10^{-4}$, 1×10^{-4}, and 3×10^{-5}, respectively (Table 4); again taking $\Omega_1^{lung} \approx 0.0024$, then $M \leq 4\%$ for the three types, as well as any mix thereof. These M values are quite low. Moreover, even when the subΣ risk for *all measured* carcinogens (i.e., $\overline{ILCR_1}^{sub\Sigma}$) is substituted for $\overline{ILCR_1}^{sub\Sigma-lung}$ in Eq. N, then the percent match values for R, Lt, and ULt cigarettes are ≤8% by CSF set I and ≤21% by CSF set II.

Another definition of the risk match for lung cancer is obtained as follows. $ILCR_z^{obs\Sigma-lung}$ is defined here as the observed average risk for an individual for z pack-years. (No distinction is made at this level of analysis on whether or not the smoker then quits.) $ILCR_z^{obs\Sigma-lung}/z$, which carries the same units as Ω_1^{lung}, then becomes the corresponding average per pack-year risk, and

$$M'\ (\%) \equiv \frac{(\overline{ILCR_1}^{sub\Sigma-lung})_{conv}}{ILCR_z^{obs\Sigma-lung}/z} \times 100\% \qquad (O)$$

is defined as a z-dependent definition of the risk match. Because of the "concave-up" nature of the nonlinearity in the dependence of lung-cancer risk on z (16, 19), much of the risk for a population that is incorporated in Ω_1^{lung} is due to those individuals with z values that are relatively large (e.g., $z > 30$). For lower z values, it can be expected that $ILCR_z^{obs\Sigma-lung}/z < \Omega_1^{lung}$ so that for such z values, M' for a particular type of conventional cigarette will be larger than the corresponding M value. Using

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[4] J.F. Pankow, K.H. Watanabe, D.F. Austin. Lung cancer incidence rate as related to cigarette consumption rate for 61 nations: the revolver model of lung cancer risk. Submitted for publication, 2007.

the 12-year follow-up data for Cancer Prevention Survey I conducted by the American Cancer Society (57) for the United States, Watanabe et al.[5] have calculated $ILCR_z^{obs\Sigma-lung}/z$ values for men and women combined. For all three types of conventional cigarettes, for $z = 10$, 15, and 20 pack-years, all $M' \le 4.5\%$ (CSF set I) and all $M' \le 9\%$ (CSF set II).

Overall, even allowing for some differences between machine and representative human smoking conditions (see above), the match values obtained here indicate that the subΣ−lung estimates of cancer risk from conventional cigarettes that can currently be calculated are either (*a*) too low (e.g., as due to incorrect CSF values) or (*b*) quite incomplete due to incomplete consideration of the roles of important carcinogens, cancer promoters, and/or irritant chemicals that promote cell proliferation as described by Preston-Martin et al. (24). These results are consistent with the conclusion of Fowles and Dybing (29) that the total estimatable cancer risk from the average conventional cigarette is much less than the observed smoking-related mortality risk for all cancers.

Risk Reduction Offered by a PREP. For a given PREP, R_{PREP} (%) is defined as the amount by which the calculatable per pack-year risk of lung cancer is reduced by switching from a particular type of conventional cigarette to that PREP:

$$R_{PREP}\ (\%) \equiv \frac{(\overline{ILCR_1^{sub\Sigma-lung}})_{conv} - (ILCR_1^{sub\Sigma-lung})_{PREP}}{\Omega_{1,lung}}$$

$$\times 100\% \ \le \ M \qquad (P)$$

The reduction in the risk can be no greater than the risk that can be accounted for with the type of conventional cigarette of interest, hence $R_{PREP} \le M$, as noted in Eq. P. The largest R_{PREP} (and M) values will result when $(\overline{ILCR_1^{sub\Sigma-lung}})_{conv}$ pertains to R cigarettes, which by CSF set I is 5×10^{-5} (Table 3) and by CSF set II is 1×10^{-4} (Table 4). With $\Omega_1^{lung} \approx 0.0024$, for each of the individual PREP cigarettes (see Supplementary Table S2D for CSF set I and Supplementary Table S3D for CSF set II), all resulting R_{PREP} values are <2% (CSF set I) and ≤4% (CSF set II). And, even when R_{PREP} values are calculated using the subΣ risk for *all measured* carcinogens - some of which will probably not be human lung carcinogens (i.e., $\overline{ILCR_1^{sub\Sigma}}$ is substituted for $\overline{ILCR_1^{sub\Sigma-lung}}$ in Eq. P, all risk reductions relative to Ω_1^{lung} are ≤8% (CSF set I) and ≤21% (CSF set II).

By analogy with Eq. O, we also define

$$R'_{PREP}\ (\%) \equiv \frac{(\overline{ILCR_1^{sub\Sigma-lung}})_{conv} - (ILCR_1^{sub\Sigma-lung})_{PREP}}{ILCR_z^{obs\Sigma-lung}/z}$$

$$\times 100\% \ \le \ M' \qquad (Q)$$

Based on the results of Watanabe et al.,[5] for $z = 10$, 15, and 20 pack-years, we obtain all $R'_{PREP} \le 4.5\%$ (CSF set I) and ≤9% (CSF set II).

Overall, the R_{PREP} and R'_{PREP} results indicate that there is not sufficient justification for viewing any PREP versions considered here (including the currently available Eclipse) as providing predicted reductions in the risk of human lung cancer that are significant relative to the observed risk for cigarettes as they are smoked by populations and quantified by Ω_1^{lung} and $\overline{ILCR_z^{obs\Sigma-lung}}/z$.

Conclusions

The risk assessment framework provides a useful means to begin the work of considering the toxicant-specific aspects of

the cancer risks of smoking cigarettes. This framework allows connections to be made between the levels of carcinogens in cigarette smoke and the observed health risks of smoking. However, for conventional cigarettes (i.e., R, Lt, and ULt cigarettes), as they are smoked by populations such as the United States and Canada, the lung carcinogen results obtained here indicate that, currently, it is only possible to account for ≤4% of the observed per pack-year risk for lung cancer. This is based on an estimate of the observed average per pack-year risk (Ω_1^{lung}) for North American smokers that has been estimated using several different approaches, all of which are highly consistent with $\Omega_1^{lung} \approx 0.0024$.

Needed improvements in the toxicant-specific risk assessment modeling of tobacco smoke include (*a*) more analytic information on the identities and levels of the myriad toxicants present in cigarette smoke by cigarette type and brand; (*b*) more complex risk models that allow consideration of the nonlinearity of the dose response, effects of carcinogen mixtures, and the roles of cancer promoters; and (*c*) high-quality toxicity data for additional toxicants.

The current inability to use toxicant-specific methods to account for the observed cancer risks of smoking carries an important implication for PREP cigarettes. Namely, all expressed and implied promises of ''reduced harm'' that now accompany the marketing of PREPs (including ostensible PREPs) must be viewed as speculative and unverified. Indeed, because dose considerations for known tobacco smoke lung carcinogens account for ≤4% of the lung cancer risk of conventional cigarettes as they are smoked by North American populations, then lowered levels of these toxicants in PREPs still leave PREPs in the possible position of being as harmful as conventional cigarettes. Expressed another way, even if a PREP design were to succeed in removing all currently measured known human lung carcinogens from cigarette smoke (and even perhaps all other currently measured carcinogens), there would be little reason to be confident that such removal would by itself lead to any observable reduction in smoking related lung cancer.

References

1. U.S. Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.
2. International Agency for Research on Cancer. Tobacco smoke and involuntary smoking. Lyon (France): IARC Press; 2004.
3. Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. J Natl Cancer Inst 2000;92:106–11.
4. Borgerding MF, Bodnar JA, Wingate DE. The 1999 Massachusetts benchmark study, final report. A research study conducted after consultation with the Massachusetts Department Public Health; 2000 July 24.
5. Gertner J. Incendiary device. New York Times Magazine 2005;154:44–51.
6. Brown and Williamson Tobacco Company. Advance Light Kings insert. 2002. Available from: http://www.fda.gov/ohrms/dockets/dailys/02/jun02/061802/8004859c.pdf. Accessed 2005 Dec 20.
7. R.J. Reynolds Tobacco Co. Available from: http://www.eclipse.rjrt.com. Accessed 2005 Dec 20.
8. Hughes JR, Hecht SS, Carmella SG, Murphy SE, Callas P. Smoking behaviour and toxin exposure during six weeks use of a potential reduced exposure product: Omni. Tobacco Control 2004;13:175–9.
9. Shiffman S, Pillitteri JL, Burton SL, Di Marino ME. Smoker and ex-smoker reactions to cigarettes claiming reduced risk. Tobacco Control 2004;13:78–84.
10. Cummings KM. Tobacco risk perceptions and behavior: implications for tobacco control. Nicotine Tob Res 2004;6 Suppl 3:S285–8.
11. Burns DM, Major JM, Shanks TG, Thun MJ, Samet JM. Smoking lower yield cigarettes and disease risks. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, editors. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2001. p. 65–158.
12. Final Opinion, United States District Court for the District of Columbia, United States of America (Plaintiff) V. Philip Morris USA, Inc. et al. (Defendants), August 17, 2006.

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[5] K.H. Watanabe, J.F. Pankow, S.D. Stellman, D.F. Austin, unpublished data, 2006.

13. Benowitz NL. Compensatory smoking of low-yield cigarettes. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, editors. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2001. p. 39–64.

14. Hammond D, Fong GT, Cummings KM, Hyland A. Smoking topography, brand switching, and nicotine delivery: results from an *in vivo* study. Cancer Epidemiol Biomarkers Prev 2005;14:1370–5.

15. Wartenberg D, Simon R. Comment: integrating epidemiologic data into risk assessment. Am J Public Health 1995;85:491–3.

16. Doll R, Peto R. Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiol Community Health 1978;32:303–13.

17. Villeneuve PJ, Mao Y. Lifetime probability of developing lung cancer, by smoking status, Canada. Can J Public Health 1994;85:385–8.

18. Holowaty E, Cheong SC, Di Cori S, et al. Tobacco or health in Ontario: tobacco-attributed cancers and deaths over the past 50 years . . . and the next 50. Toronto (Ontario): Division of Preventive Oncology, Cancer Care Ontario; 2002.

19. Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. J Natl Cancer Inst 2003;95:470–8.

20. U.S. Environmental Protection Agency. Risk assessment guidance for Superfund. Volume 1. Human health evaluation manual (part A), interim final. Washington (DC): Office of Emergency and Remedial Response; 1989. Report no. EPA/540/1-89/002.

21. U.S. EPA. Guidelines for the health risk assessment of chemical mixtures. Federal Register 1986;51:34014–25.

22. U.S. EPA. Guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity. Washington (DC): Office of Pesticide Programs, U.S. Environmental Protection Agency; 2002.

23. Burkart W, Jung T. Health risks from combined exposures: mechanistic considerations on deviations from additivity. Mutat Res 1998;411:119–28.

24. Preston-Martin S, Pike MC, Ross RK, Henderson BE. Epidemiologic evidence for the increased cell proliferation model of carcinogenesis. Chemically induced cell proliferation: implications for risk assessment. Wilmington (DE): Wiley-Liss; 1991. p. 21–34.

25. Zhou W, Thurston SW, Liu G, et al. The interaction between microsomal epoxide hydrolase polymorphisms and cumulative cigarette smoking in different histological subtypes of lung cancer. Cancer Epidemiol Biomarkers Prev 2001;10:461–6.

26. Thurston SW, Liu G, Miller DP, Christiani DC. Modeling lung cancer risk in case-control studies using a new dose metric of smoking. Cancer Epidemiol Biomarkers Prev 2005;14:2296–302. Erratum in: Cancer Epidemiol Biomarkers Prev 2005;14:3020.

27. Siemiatycki J. Synthesizing the lifetime history of smoking. Cancer Epidemiol Biomarkers Prev 2005;14:2294–5.

28. Vorhees DJ, Dodson RE. Estimating risk to cigarette smokers from smoke constituents in proposed ''Testing and Reporting of Constituents of Cigarette Smoke'' Regulations. Boston (MA): Menzie-Cura & Associates, Inc.; 1999.

29. Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. Tobacco Control 2003;12:424–30.

30. Kozlowski LT, O'Connor RJ, Sweeney CT. Cigarette design. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, editors. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2001. p. 13–38.

31. U.S. Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A report of the Surgeon General. Rockville (MD): U.S. Department of Health and Human Services Publication no. (CDC) 88-8406; 1988.

32. Lee EM, Malson JL, Moolchan ET, Pickworth WB. Quantitative comparisons between a nicotine delivery device (Eclipse) and conventional cigarette smoking. Nicotine Tob Res 2004;6:95–102.

33. Roemer E, Stabbert R, Rustemeier K, et al. Chemical composition, cytotoxicity and mutagenicity of smoke from US commercial and reference cigarettes smoked under two sets of machine smoking conditions. Toxicology 2004;195:31–52.

34. Borgerding MF, Bodnar JA, Chung HL, et al. Chemical and biological studies of a new cigarette that primarily heats tobacco. Part 1. Chemical composition of mainstream smoke. Food Chem Toxicol 1997;36:169–82.

35. Stabbert R, Voneken P, Rustemeier K, et al. Toxicological evaluation of an electrically heated cigarette. Part 2. Chemical composition of mainstream smoke. J Appl Toxicol 2003;23:329–39.

36. R.J. Reynolds Inc. Eclipse. A cigarette that primarily heats, rather than burns, tobacco. Summary of scientific tests: R. J. Reynolds Tobacco Company; 2000 April.

37. Hoffmann D, Hoffmann I. The changing cigarette: chemical studies and bioassays. In: Shopland DR, Burns DM, Benowitz NL, Amacher RH, editors. Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine. Bethesda (MD): U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2001. p. 159–92.

38. Slade J, Connolly GN, Lymperis D. Eclipse: does it live up to its health claims? Tobacco Control 2002;11:64–70.

39. Byrd GD, Fowler KW, Hicks RD, Lovette ME, Borgerding MF. Isotope dilution gas chromatography-mass spectrometry in the determination of benzene, toluene, styrene and acrylonitrile in mainstream cigarette smoke. J Chromatog 1990;503:359–68.

40. Borgerding MF, Fowler KW, Rogers JC. Chemical characterization of the mainstream smoke from XDU cigarette prototype 2-104—a summary. Feb 25, 1993. Bates no. 510259737/9765. Available from: http://legacy.library. ucsf.edu/tid/gkh63d00.

41. Anon. Mainstream smoke yields—benzene. Bates no. 510941672. Available from: http://legacy.library.ucsf.edu/tid/pty90d00.

42. Rogers JC, Fowler KW, Parsons SV, Jordan FD. Comparison of mainstream smoke from XDU (DS021492-1, 6239), Premier, and German Reference R1 cigarettes by gas chromatography with mass selective detection. Bates no. 512826632/6642. Available from: http://legacy.library.ucsf.edu/tid/abz23d00. Accessed 2005 Feb 8. R.J. Reynolds collection; 1993.

43. Rogers JC, Winkler LS, Fowler KW. Comparison of benzene and toluene concentrations in mainstream smoke from XDU 740, Premier, and German Reference R1 cigarettes by gas chromatography with selected ion monitoring detection. Bates no. 510941680/1692. Available from: http://legacy.library.ucsf.edu/tid/gbp53d00. Accessed 2003 Jan 22.

44. U.S. Environmental Protection Agency. Integrated Risk Information System. In: Office of Research and Development, National Center for Environmental Assessment; 2003.

45. California Environmental Protection Agency. All chronic reference exposure levels adopted by OEHHA as of August 2003. Available from: http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html. Accessed 2005 Jan 12.

46. California Environmental Protection Agency. September 2004-OEHHA cancer potency list. 2004. Available from: http://www.oehha.ca.gov/risk/ChemicalDB/index.asp. Accessed 2005 Apr 6.

47. California Environmental Protection Agency. Expedited cancer potency values and no significant risk levels (NSRLs) for six proposition 65 carcinogens: carbazole, MeIQ, MeIQx, methyl carbamate, 4-*N*-nitrosome-thylamino)-1-(3-pyridyl)-1-butanone, trimethyl phosphate. Sacramento (CA): Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment; 2001.

48. Surgeon General. Reducing the health consequences of smoking: 25 years of progress. Washington (DC): U.S. Gov Print Off; 1989.

49. Imperial Tobacco Ltd. Measurement of cigarette smoke components of six Imperial Tobacco cigarette brands sold in British Columbia. As cited in Vorhees and Dodson (28).

50. U.S. Environmental Protection Agency. Air Toxics Risk Assessment Reference Library Volume 1. Technical Resource Manual. Research Triangle Park (NC): Office of Air Quality Planning and Standards; 2004. Report no. EPA-453-K-04-001A.

51. Shopland DR. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. Environ Health Perspect 1995; 103 Suppl 8:131–42.

52. GLOBOCAN 2002, Software and Database Version 2.0, September 2004. Available from: http://www-dep.iarc.fr/. Accessed 2005 Dec 20.

53. Statistics Canada. Available from: http://www40.statcan.ca/. Accessed 2005 Dec 20.

54. Gilmore J. Report on smoking in Canada. Ottawa, Ontario (Canada): Health Statistics Division, Statistics Canada Minister of Industry; 2002.

55. Canadian Council for Tobacco Control, National Clearinghouse on Tobacco and Health. Production of tobacco products. Available from: http://www.ncth.ca/NCTH_new.nsf. Accessed 2005 Dec 20.

56. Centers for Disease Control, National Center for Chronic Disease Prevention and Health Promotion. Available from: http://www.cdc.gov/tobacco/who/canada.htm. Accessed 2005 Dec 20.

57. National Cancer Institute. Changes in Cigarette-related disease risks and their implication for prevention, 97-4213. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health; 1997.

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