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Incremental lifetime cancer risks computed for benzo[a]pyrene and two tobacco-specific *N*-nitrosamines in mainstream cigarette smoke compared with lung cancer risks derived from epidemiologic data

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ABSTRACT

The manner in which humans smoke cigarettes is an important determinant of smoking risks. Of the few investigators that have predicted cancer risks from smoking on a chemical-specific basis, most used mainstream cigarette smoke (MCS) carcinogen emissions obtained via machine smoking protocols that only approximate human smoking conditions. Here we use data of Djordjevic et al. [Djordjevic, M.V., Stellman, S.D., Zang, E., 2000. Doses of nicotine and lung carcinogens delivered to cigarette smokers. J. Natl. Cancer Inst. 92, 106–111] for MCS emissions of three carcinogens measured under human smoking conditions to compute probability distributions of incremental lifetime cancer risk (ILCR) values using Monte Carlo simulations. The three carcinogens considered are benzo[a]pyrene, *N*′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Computed NNK ILCR values were compared with lifetime risks of lung cancer ($ILCR_{CMD}^{obs\Sigma-lung}$) derived from American Cancer Society Cancer Prevention Studies (CPS) I and II. Within the Monte Carlo simulation results, NNK was responsible for the greatest ILCR values for all cancer endpoints: median ILCR values for NNK were ~18-fold and 120-fold higher than medians for NNN and benzo[a]pyrene, respectively. For "regular" cigarettes, the NNK median ILCR for lung cancer was lower than $ILCR_{CMD}^{obs\Sigma-lung}$ from CPS-I and II by >90-fold for men and >4-fold for women. Given what is known about chemical carcinogens in MCS, this study shows that there is a higher incidence of lung cancer from exposure to MCS than can be predicted with current risk assessment methods using available toxicity and emission data.

1. Introduction

As early as the 1950s, smoking was recognized as a risk factor for lung cancer (Doll and Hill, 1950, 1954, 1956; Wynder and Graham, 1950; Hammond and Horn, 1958a,b), and later became associated with many other respiratory and cardiovascular diseases (US Department of Health and Human Services, 1964). Nevertheless, though smoking prevalence in adults has decreased significantly in the United States since the first US Surgeon General Report in 1964 (from 42% in 1965 to 21% in 2004) (Centers for Disease Control and Prevention, 2005), it is not decreasing at a rate that will meet the goal of 12% set in Healthy People 2010 (US Department of Health and Human Services, 2000). Unfortunately, it is difficult to quit smoking (Hughes et al., 2004) and various types of new tobacco products have been introduced in the last decades with explicit and/or implied promises of greater relative safety (Stratton et al., 2001), e.g., "light" and "ultralight" cigarettes as well as newer "potentially reduced exposure product" (PREP) cigarettes such as the Eclipse™. Epidemiologic determination of the health risks of a given type of cigarette may only be possible after smokers have been exposed to the product for at least 20 years. For example, approximately 30 years after the introduction of "light" cigarettes in the 1970s, recent reports (National Cancer Institute, 2001; Harris et al., 2004) have described the failure of "light" (6 ⩽ Federal Trade Commission (FTC) tar content

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Nomenclature

Term	Meaning (Units)
A^i	Chemical i emission per cigarette (ng/cig)
ACS	American Cancer Society
ANOVA	analysis of variance
AT	averaging time (days)
BaP	benzo[a]pyrene
BW	body weight (kg)
Cd	cadmium
CDF	cumulative distribution function
CD_z^i	average (chronic) rate of daily intake of carcinogen i from smoking when the total smoking dose is z pack-years and, in this work, when the dose is averaged over 75 years (mg/kg-day)
CF	conversion factor (10^{-6} mg/ng)
CIR_{CMD}	cumulative lung cancer incidence rate per 100,000 PYO
CMD	cumulative mortality for all exposure durations
CMR_{CMD}	cumulative lung cancer mortality rate per 100,000
$CPS\text{-}I^{6y}$	Cancer Prevention Study I, six-year follow-up (1960 to 1966)
$CPS\text{-}I^{12y}$	Cancer Prevention Study I, 12-year follow-up (1960 to 1972)
$CPS\text{-}II^{6y}$	Cancer Prevention Study II six-year follow-up (1982 to 1988)
CSF^i	cancer slope factor for carcinogen i (also known as the "cancer potency" of i) $(mg/kg\text{-}day)^{-1}$
ED	exposure duration (years)
EF	exposure frequency (days/year)
FTC	Federal Trade Commission
i	a carcinogen of interest: BaP, NNN, or NNK
IARC	International Agency for Research on Cancer
$ILCR_z^i$	incremental lifetime cancer risk for carcinogen i for a smoking dose of z pack-years (risk for z pack-years)
$\overline{ILCR}_z^i$	Average of $ILCR_z^i$ values (risk for z pack-years)
$\overline{ILCR}_z^{i-MC}$	Average of Monte Carlo simulated $ILCR_z^i$ values
$ILCR_{CMD}^{obs\Sigma-lung}$	The incremental lifetime risk of being diagnosed with lung cancer derived from epidemiologic data
$ILCR_z^{NNK-lung}$	incremental lifetime cancer risk for lung cancer from exposure to NNK
LR_{CMD}	lifetime risk of being diagnosed with lung cancer
MC	Monte Carlo
MCS	mainstream cigarette smoke
NHANES	National Health and Nutrition Examination Survey
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	*N*′-nitrosonornicotine
PREP	potentially reduced exposure product
PYO	person-years of observation
ρ	Pearson's correlation coefficient
RIAGENDR	NHANES subject gender
RIDAGEYR	NHANES subject age (years)
SEER	Surveillance, Epidemiology and End Results
SMD030	NHANES subject age at onset of smoking (years)
SMD070	NHANES subject average number of cigarettes smoked per day (cig/day)
SMQ040	NHANES—whether or not the subject now smokes
$\overline{SR}$	average number of cigarettes smoked per day (aka smoking rate or smoking intensity) (cig/day)
z	smoking dose or total number of cigarettes smoked (pack-years)

(mg/cig) < 15) and "ultralight" (FTC tar < 6 mg/cig) cigarettes to reduce smoking-related disease. Therefore, more expeditious methods of evaluating risks from currently marketed and PREP cigarette products are needed, and one possible approach is to compute risks on a toxicant-specific basis.

A few studies (Vorhees and Dodson, 1999; Fowles and Dybing, 2003; Pankow et al., 2007) implement methods to assess toxicant-specific risks of mainstream cigarette smoke (MCS) from different brands and types of cigarettes. Vorhees and Dodson (1999) first applied regulatory risk assessment methodology (US Environmental Protection Agency, 2005) to compute incremental (excess) lifetime cancer risks (ILCR) and non-cancer hazard quotients for 71 chemicals measured in MCS of 25 different cigarette brands, although not all chemicals were measured in all cigarette brands. They found 19 carcinogens (e.g., carcinogenic polycyclic aromatic hydrocarbons, nitrosamines, and hydrazine) with chemical-specific cancer risks greater than 10^{-6} for a smoking dose of 30 pack-years (=20 cigarettes (one pack) per day for 30 years). An ILCR value of 10^{-6} is the probability that 1 person may develop cancer out of 1,000,000 people exposed to a carcinogen (US Environmental Protection Agency, 1991), and it is a commonly referenced benchmark for the protection of public health (US Environmental Protection Agency, 2004a,b). Fowles and Dybing (2003) assembled data on 158 chemical constituents (including 41 carcinogens) in MCS from published sources and developed a toxicological risk prioritization index. They concluded that toxicological risk assessment methods provide a sound basis for prioritizing chemical toxicants in MCS, but also noted that estimates of actual cancer risks are complicated by differences in toxicant emissions from cigarettes obtained by machine smoking protocols vs. emissions that result under typical human smoking conditions. Pankow et al. (2007) utilized available emission data obtained with machine smoking protocols to assess carcinogen-specific ILCR values for 13 chemical carcinogens measured in MCS from 26 brands of conventional cigarettes categorized as "regular", "light", and "ultralight", and from eight brands of PREP cigarettes. Cancer risks were calculated for an assumed smoking dose of one pack-year (=7300 cigarettes), a body weight of 70 kg, and a 70-year lifetime. Cumulative risks of exposure to the 13 carcinogens were computed for each brand following an additive model (US Environmental Protection Agency, 1986; Krewski and Thomas, 1992). For all categories of cigarettes, at one pack-year, some carcinogen-specific risks and cumulative risks exceeded 10^{-6} (Pankow et al., 2007) .

The three prior toxicant-specific risk investigations (Vorhees and Dodson, 1999; Fowles and Dybing, 2003; Pankow et al., 2007) used MCS chemical emissions measured by machine smoking protocols, assumed constant values for parameters such as smoking rate and body weight, and followed a deterministic approach for calculating risks. It is known, however, that a wide variety of smoking habits and histories will be found in any given population of smokers, and that there are gender differences in smoking habits and body weight distributions (National Center for Health Statistics, 2005b; Melikian et al., 2007). As an extension of these earlier studies, we performed a probabilistic analysis of risks that accounts for uncertainty and variability in the way people smoke cigarettes. Such an analysis requires population distributions of MCS carcinogen emissions, smoking habits and histories.

Of 69 known carcinogens in MCS (International Agency for Research on Cancer, 2004), Djordjevic et al. (2000) measured BaP, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and *N*′-nitrosonornicotine (NNN, unpublished) under human smoking conditions. Though the data reported by Djordjevic et al. for 133 subjects are a subset of a larger dataset for 257 subjects recently

published by Melikian et al. (2007), we believe that the 133 subjects are representative of the larger dataset for important parameters such as smoking rate, duration, and the type of cigarette smoked. BaP is a polycyclic aromatic hydrocarbon (Stellman and Guidotti, 2006) classified as a human carcinogen by the International Agency for Research on Cancer (IARC) (Straif et al., 2005) based on animal studies. NNN and NNK are tobacco-specific nitrosamines that are also classified as human carcinogens by IARC (Cogliano et al., 2004) based on animal studies. Of the 13 carcinogen-specific ILCR values computed by Pankow et al. (2007) for "regular" cigarettes and one pack-year of smoking, BaP, NNN, and NNK have ILCR values of 5×10^{-7} (11th highest), 2×10^{-6} (9th highest), and 4×10^{-5} (2nd highest), respectively.

In this study, we use BaP, NNN, and NNK emissions measured under human smoking conditions, years of smoking, and the number of cigarettes smoked per day from Djordjevic et al. (2000), smoker body weight data from the National Health and Nutrition Examination Survey (NHANES) (2005b), and a Monte Carlo (MC) method (US Environmental Protection Agency, 2001) to simulate distributions of ILCR values. Other MCS carcinogens were not considered in this study because emission measurements under human smoking conditions were unavailable for individual smokers and a sample size comparable to that of Djordjevic et al. To quantitatively evaluate how well carcinogen-specific ILCR values predict lung cancer risks derived epidemiologically, we compare MC-simulated risks with lifetime lung cancer risks computed here for the first time from two American Cancer Society epidemiological studies, Cancer Prevention Studies (CPS) I and II.

2. Methods

Pankow et al. (2007) used risk assessment methodology (US Environmental Protection Agency, 2005) to determine incremental lifetime cancer risk ($ILCR_z^i$) values for chemical carcinogen, i, in MCS as a function of the smoking dose z (pack-years).

$$ILCR_z^i = CDI_z^i \times CSF^i, \tag{1}$$

where CDI_z^i (mg/kg-day) is the chronic daily intake (i.e., average daily dose, or total intake from the number of years of smoking averaged over an expected lifespan); and CSF^i $(mg/kg\text{-}day)^{-1}$ is the cancer slope factor (aka cancer potency (California Environmental Protection Agency, 2001, 2004)). Slight modification of the equations in Pankow et al. gives

$$ILCR_z^i = \frac{A^i \times \overline{SR} \times EF \times ED \times CF}{BW \times AT} \times CSF^i = \frac{A^i \times 7300 \times z \times CF}{BW \times 27,375} \times CSF^i, \tag{2}$$

where A^i is chemical emission per cigarette (ng/cig); $\overline{SR}$ is the average number of cigarettes smoked per day (cig/day); EF is exposure frequency (=365 days/year in this study); ED is exposure duration (years of smoking); CF is a conversion factor (10^{-6} mg/ng); BW is body weight (kg); AT is an averaging time (days) following US EPA (US Environmental Protection Agency, 1989); and CSF^i $(mg/kg\text{-}day)^{-1}$ is the cancer slope factor (aka cancer potency (California Environmental Protection Agency, 2001, 2004)). We departed from US EPA guidance of a 70-year median human lifespan for AT and instead used 75 years (27,375 days) to be consistent with increasing life expectancy in the US (National Center for Health Statistics, 2005a). Multiplication of $\overline{SR}$, EF, ED divided by 7300 cigarettes per pack-year yields $ILCR_z^i$ as a function of z (pack-years). Eq. (2) is a linear model where an equivalent $ILCR_z^i$ value will be predicted for values of z that may be obtained in multiple ways, i.e., $z = 1$ pack-year can be achieved by smoking one cigarette per day for 20 years, or 20 cigarettes (one pack) per day for 1 year. Furthermore, the same $ILCR_z^i$ value will be predicted for former smokers and current smokers who smoke the same number of pack-years. In this study, A^i, $\overline{SR}$, ED, and BW were treated as random variables to compute distributions of $ILCR_z^i$ values; CSF^i, EF, CF and AT were assumed to remain constant.

2.1. Characterization of Djordjevic et al. (2000) data

Djordjevic et al. (2000) studied the smoking topography of 133 users of low-nicotine and medium-nicotine yield cigarettes to determine MCS emissions of selected carcinogens and toxicants under actual human smoking conditions. For each subject, recorded data included $\overline{SR}$, ED, BW, brand of cigarette with information about size, type of pack, whether mentholated or not, and FTC tar yield for the cigarette. For all 133 subjects, smoking parameters such as puff volume, puff duration, interval between puffs, butt length, and the degree of filter ventilation hole blocking were determined. Then, for a randomly selected subset of 72 subjects, smoking parameters were programmed into a smoking machine to produce MCS samples from each subject's brand of cigarette. The MCS samples were analyzed for emissions of nicotine, carbon monoxide, tar, BaP, NNK, and NNN; NNN data were not published in Djordjevic et al. (2000).

We categorized cigarettes based upon FTC tar yields (Kozlowski et al., 2001) as: "regular", $\geqslant$15 mg tar/cig; "light", 6 mg tar/cig to <15 mg tar/cig; or "ultralight", 1 mg tar/cig to <6 mg tar/cig. Six of the 133 subjects in Djordjevic et al. smoked "ultralight" cigarettes, and toxicant emissions were measured using the smoking topography of only one of those six subjects. Because of the limited toxicant emission data for "ultralight" cigarettes, we did not consider this cigarette type in our analysis.

Table 1 summarizes the data from Djordjevic et al. pertaining to the three carcinogens of interest along with the CSF^i values that were used to compute $ILCR_z^i$ for 71 (=72 − 1) subjects. Pearson's chi-squared and Yate's corrected chi-squared (for small sample sizes) tests were used to compare $\overline{SR}$, ED, BW, and A^i in men and women separately in order to determine parameter independence which is important for the MC simulations (Bois et al., 1991; Spear et al., 1991; Woodruff et al., 1992; Watanabe et al., 1994) discussed below. All parameters were found to be independent of each other except for A^{NNN} and A^{NNK}. However, a lack of independence among A^i values does not affect the use of the MC method because the MC simulations were run separately for each carcinogen. Lognormal distributions were fitted to the measurements of A^{BaP}, A^{NNN} and A^{NNK} grouped by gender and the type of cigarette smoked ("regular" or "light") using Systat® 11 (see Table 1).

An analysis of variance (ANOVA) was performed to determine whether we could combine $\overline{SR}$ values for "regular" and "light" cigarettes and both genders. No significant differences were found between the means for male smokers of "regular" ($n = 36$), and "light" ($n = 24$) cigarettes, and female smokers of "regular" ($n = 32$), and "light" ($n = 35$) cigarettes. Thus, 127 $\overline{SR}$ values (both genders and two cigarette types) were combined, and Systat® 11 was used to fit a lognormal distribution to the data. Similarly for ED values, an ANOVA was performed that resulted in no significant differences based on gender or the type of cigarette smoked. Thus, ED values for male and female smokers of "regular" and "light" cigarettes were combined and a normal distribution was found to fit the data best (Table 1). The normal distribution was truncated at zero and 50 years to be consistent with observations from Djordjevic et al. Continuous distributions were fit to the $\overline{SR}$ and ED data because these variables are likely to have a continuous range of values in a population of smokers, whereas when surveyed, smokers report whole numbers of cigarettes smoked per day and years of smoking.

Table 1
Summary statistics (μ = mean; σ = standard deviation) for toxicant emissions, smoking rates and exposure durations from Djordjevic et al. (2000), and parameter definitions and distributions used to compute $ILCR_z^i$ through Monte Carlo simulation. BaP = benzo[a]pyrene; NNK = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; and NNN = *N*′-nitrosonornicotine.

Parameter	Definition	"Regular" cigarettes		"Light" cigarettes		Reference
		Male smokers	Female smokers	Male smokers	Female smokers	
CSF^{BaP}	BaP cancer slope factor $(mg/kg\text{-}day)^{-1}$	3.9	3.9	3.9	3.9	California Environmental Protection Agency (2004)
CSF^{NNN}	NNN cancer slope factor $(mg/kg\text{-}day)^{-1}$	1.4	1.4	1.4	1.4	California Environmental Protection Agency (2004)
CSF^{NNK}	NNK cancer slope factor $(mg/kg\text{-}day)^{-1}$	49	49	49	49	California Environmental Protection Agency (2001)
EF	Exposure frequency (days/year)	365	365	365	365	
CF	Conversion factor (mg/ng)	10^{-6}	10^{-6}	10^{-6}	10^{-6}	
AT	Averaging time (days)	27,375[a]	27,375[a]	27,375[a]	27,375[a]	
A^{BaP}	BaP emission (ng/cig)	$n = 23$	$n = 14$	$n = 15$	$n = 19$	Djordjevic et al. (2000)
	μ (σ)	25 (10)	20 (4.4)	20 (13)	21 (6.6)	Djordjevic et al. (2000)
	Median	23	19	16	18	Djordjevic et al. (2000)
	Distribution[b]	LN(3.1, 0.41)	LN(3.0, 0.21)	LN(2.8, 0.54)	LN(3.0, 0.32)	this study
A^{NNK}	NNK emission (ng/cig)	$n = 23$	$n = 14$	$n = 15$	$n = 19$	Djordjevic et al. (2000)
	μ (σ)	271 (139)	280 (83)	207 (97)	216 (92)	Djordjevic et al. (2000)
	Median	215	292	212	193	Djordjevic et al. (2000)
	Distribution[b]	LN(5.5, 0.42)	LN(5.6, 0.31)	LN(5.2, 0.55)	LN(5.3, 0.42)	this study
A^{NNN}	NNN emission (ng/cig)	$n = 23$	$n = 14$	$n = 15$	$n = 19$	Djordjevic et al. (2000)
	μ (σ)	468 (150)	488 (135)	340 (168)	359 (140)	Djordjevic et al. (2000)
	Median	452	446	283	335	Djordjevic et al. (2000)
	Distribution[b]	LN(6.1,0.32)	LN(6.2,0.28)	LN(5.7, 0.51)	LN(5.8, 0.39)	this study
$\overline{SR}$	Average smoking rate (cig/day)	$n = 36$	$n = 32$	$n = 24$	$n = 35$	Djordjevic et al. (2000)
	μ (σ)	19 (9.7)	17 (8.7)	19 (15)	16 (5.8)	Djordjevic et al. (2000)
	Median	17	16	15	15	Djordjevic et al. (2000)
	Distribution[b]	LN(2.7, 0.47)	LN(2.7, 0.47)	LN(2.7, 0.47)	LN(2.7, 0.47)	this study
ED	Exposure duration (years)	$n = 36$	$n = 32$	$n = 24$	$n = 35$	Djordjevic et al. (2000)
	μ (σ)	21 (9.8)	19 (11)	21 (12)	19 (12)	Djordjevic et al. (2000)
	Median	20	19	20	19	Djordjevic et al. (2000)
	Distribution[b]	TN(20, 11, 0, 50)	TN(20, 11, 0, 50)	TN(20, 11, 0, 50)	TN(20, 11, 0, 50)	this study
BW	Body weight (kg)	$n = 36$	$n = 32$	$n = 24$	$n = 35$	Djordjevic et al. (2000)
	μ (σ)	82 (13)	69 (15)	82 (18)	62 (11)	Djordjevic et al. (2000)
	Median	84	66	82	59	Djordjevic et al. (2000)
	Distribution[b]	LN(4.4, 0.23)	LN(4.3, 0.25)	LN(4.4, 0.23)	LN(4.3, 0.25)	National Center for Health Statistics (2005b)

[a] Averaging time 75 years × 365 days/year.
[b] Probability distribution abbreviations: LN = lognormal (M, SD) where M = mean of log-transformed data, and SD = standard deviation of log-transformed data; TN = truncated normal (μ, σ, LB, UB) where LB and UB are the lower and upper bounds, respectively.

2.2. Distributions of BW, $\overline{SR}$, ED and z values in the US population

We obtained the following SAS® export files containing NHANES 2001–2002 data (National Center for Health Statistics, 2005b) from the Centers for Disease Control: (1) Demographic Variables and Sample Weights (demo_b.xpt) for age and gender; (2) Body Measurements (bmx_b.xpt) for body weights; (3) and Smoking and Tobacco Use (smq_b.xpt) for smoking-related data. Data were imported into a Microsoft® Access database, and related by respondent sequence number (SEQN in all tables). A query for respondent age, gender, smoking status and body weight was run, then the results were exported to Systat® 11 where lognormal distributions were fitted separately to BW of adult (age 18+ years) men and women smokers (see Table 1).

The NHANES 2001–2002 study provided an independent set of $\overline{SR}$ and ED values in "everyday" smokers (906 respondents) for evaluating our MC-simulated distributions of z. The NHANES Smoking and Tobacco Use table was queried for: (1) whether the study participant "now smokes cigarettes" (SMQ040, 1 indicates a current smoker); (2) the average number of cigarettes smoked per day (SMD070); and (3) the age at onset of smoking (SMD030). Participants' ages at the time of the survey (RIDAGEYR) and gender (RIAGENDR) were obtained from the NHANES demographics table (demo_b). Values of z were computed for "everyday" smokers (SMQ040 = 1) according to

$$z(\mathrm{SMQ040}=1)=\frac{\mathrm{SMD070}\times 365\times \mathrm{YRS\_SMOKING}}{7300}, \quad (3)$$

where, YRS_SMOKING was calculated as the difference between a respondent's age (RIDAGEYR) and their reported age at onset of smoking (SMQ030). It should be noted that this sample of "everyday" smokers may include smokers who also use other forms of tobacco, however, we do not expect this to have a large impact on our analysis. A Kruskal–Wallis test was used to test for differences between median z values from the Monte Carlo simulations, Djordjevic et al. and NHANES.

2.3. Monte Carlo simulations

Smokers in a population are exposed to varying doses of MCS carcinogens because of variability in A^i values, individual smoking habits and exposure history. To account for population variability in MCS carcinogen CDI_z^i values, a probabilistic MC simulation approach used elsewhere (Bois et al., 1991; Spear et al., 1991; Woodruff et al., 1992; Watanabe et al., 1994) was applied here. Rather than sampling z, $\overline{SR}$ and ED were sampled separately because other studies have treated $\overline{SR}$ and ED as independent variables, e.g., in the analysis of: lung cancer incidence rates from a 20-year prospective study of British doctors (Doll and Peto, 1978), lung cancer mortality rates from CPS-II (Flanders et al., 2003), and the probability of lung cancer from a case–control study (Thurston et al., 2005). MCSim software (Bois and Maszle, 1997) was used to obtain randomly sampled values of A^i, $\overline{SR}$, ED, and BW from their probability distributions and to compute $ILCR_z^i$ values.

Each iteration of an MC simulation computed an $ILCR_z^i$ value from a combination of the randomly sampled input parameters with the parameters that were held constant (e.g., AT). Thus, a total of 12 distributions were obtained, one for each combination of carcinogen (i.e., BaP, NNN, or NNK), gender, and the type of cigarette smoked (i.e., "regular" or "light"). To determine how many iterations were needed to provide a reasonable characterization of each $ILCR_z^i$ distribution, we performed 1,000, 5,000, and 100,000 iterations for male smokers of "regular" cigarettes exposed to NNK. A comparison of boxplots of CDI_z^{NNK} showed no appreciable difference in the median and 90% confidence interval of each distribution, although larger numbers of iterations provided more CDI_z^{NNK} values in the tails of the distribution (i.e., below the 10th percentile and above the 90th percentile). Thus, 1000 iterations were performed for the remaining the MC simulations.

2.4. Lifetime risks from epidemiologic studies

To evaluate the MC-simulated $ILCR_z^i$ values, we calculated $ILCR_{CMD}^{obs\Sigma-lung}$ from CPS-I and II data as documented by Smoking and Tobacco Control Monograph 8 (1997); CMD is the total number of observed deaths for all exposure durations in an attained age group. For 12 years of follow-up from 1960 to 1972 for CPS-I ($CPS\text{-}I^{12y}$), the available data include: the number of observed deaths; total person-years of observation (PYO)[1]; never-smoker mortality rates; excess mortality rates; and relative risks, all as stratified by: $\overline{SR}$ groups of 1 to 9, 10 to 19, 20, 21 to 39, and 40+ cig/day; ED groups of 0–4 years, 5–9, ..., and 75–79 years; and attained age groups of 40–44, 45–50, ..., and 80–84 years. For 6 years of follow-up from CPS-I ($CPS\text{-}I^{6y}$, 1960–1966) and CPS-II ($CPS\text{-}II^{6y}$, 1982–1988), the published data are: observed deaths; PYO; and mortality rates for never-smokers stratified by attained age from 50 to 85+ years in 5-year groups, and for smokers stratified by: $\overline{SR}$ values of 20 or 40 cig/day; ED from 30 to 50+ years in 5-year groups; and attained age from 50 to 85+ in 5-year groups.

For each $\overline{SR}$ range we computed lifetime risks of being diagnosed with lung cancer (LR_{CMD}) following Wun et al. (1998).

$$LR_{CMD}=1-\exp(-CIR_{CMD}/100{,}000), \quad (4)$$

where CIR_{CMD} is the cumulative lung cancer incidence rate per 100,000 PYO. To obtain values of CIR_{CMD}, cumulative lung cancer mortality rates (CMR_{CMD}) were computed as the sum of 5-year attained age group mortality rates (per 100,000 PYO) multiplied by 5 years per age group.

Similarly, for never-smokers, a lifetime risk, LR_0, was calculated following the procedure outlined above using mortality rates from a logistic regression model reported for $CPS\text{-}I^{12y}$ and observed never-smoker mortality rates for $CPS\text{-}I^{6y}$ and $CPS\text{-}II^{6y}$. Finally, the incremental lifetime cancer risk of being diagnosed with lung cancer ($ILCR_{CMD}^{obs\Sigma-lung}$) was computed following Eq. (5) (see Online Supplement for details).

$$ILCR_{CMD}^{obs\Sigma-lung}=LR_{CMD}-LR_0. \quad (5)$$

3. Results

Computed $ILCR_z^i$ values are reported in Table 2 for the 71 smokers of "regular" and "light" cigarettes for whom A^{BaP}, A^{NNN}, and A^{NNK} values were measured by Djordjevic et al. For a particular cigarette type, statistically significant differences exist between $ILCR_z^i$ values for BaP, NNN, and NNK (paired t-test, all Bonferroni corrected p-values <0.001), which is largely dependent upon the CSF^i value for each carcinogen. However, for each carcinogen, the $ILCR_z^i$ values are not significantly different for "regular" vs. "light" cigarettes, or by smoker gender (Online Supplement Fig. S1).

Distributions of $ILCR_z^{i-MC}$ values obtained by MC simulations (Fig. 1) followed the trends observed in the $ILCR_z^i$ values derived from the Djordjevic et al. data. While small differences were found in the simulated $ILCR_z^{i-MC}$ distributions based on gender or cigarette type for a given carcinogen, large differences exist between $ILCR_z^{i-MC}$ values for the three carcinogens (see Table 3 for summary statistics): median $ILCR_z^{NNK-MC}$ >> median $ILCR_z^{NNN-MC}$ >> median $ILCR_z^{BaP-MC}$. The means and medians of the MC-simulated

[1] Each participant is considered to contribute one person-year of observation for each year they are in the study and a half-year in the year that they die from lung cancer.

Table 2
Summary statistics of incremental lifetime cancer risks computed for 71 Djordjevic et al. (2000) study subjects. Values reported per 100,000: mean ($\overline{ILCR_z^i}$); standard deviation (σ); median; 2.5th percentile; and 97.5th percentile for benzo[a]pyrene (BaP), *N*′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). CSF^i = cancer slope factor for carcinogen *i*.

	"Regular" cigarettes		"Light" cigarettes	
Toxicant	Male smokers (n = 23)	Female smokers (n = 14)	Male smokers (n = 15)	Female smokers (n = 19)
Benzo[a]pyrene (BaP); CSF^{BaP} = 3.9 (mg/kg-day)$^{-1}$				
$\overline{ILCR_z^{BaP}}(\sigma)$	0.74 (0.87)	0.69 (0.81)	0.66 (0.78)	0.56 (0.45)
$Median^{BaP}$	0.49	0.43	0.38	0.37
2.5th percentile	0.10	0.080	0.028	0.069
97.5th percentile	3.0	2.5	2.5	1.5
N′-nitrosonornicotine (NNN); CSF^{NNN} = 1.4 (mg/kg-day)$^{-1}$				
$\overline{ILCR_z^{NNN}}(\sigma)$	4.8 (4.4)	5.7 (6.7)	3.8 (4.1)	4.0 (5.0)
$Median^{NNN}$	2.6	3.1	2.5	2.4
2.5th percentile	0.75	0.71	0.22	0.49
97.5th percentile	15	21	13	17
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK); CSF^{NNK} = 49 (mg/kg-day)$^{-1}$				
$\overline{ILCR_z^{NNK}}(\sigma)$	108 (139)	106 (108)	79 (72)	86 (113)
$Median^{NNK}$	47	78	62	49
2.5th percentile	14	15	4.4	8.2
97.5th percentile	499	348	208	374

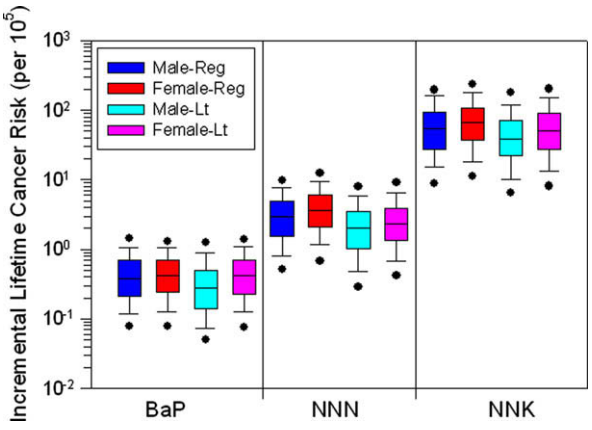


Fig. 1. Results of 1000 Monte Carlo simulated incremental lifetime cancer risks ($ILCR_z^{i-MC}$) for benzo[a]pyrene (BaP), *N*′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Constant values used in calculations: EF = 365 days; CF = 10^{-6} mg/ng; and AT = 27,375 days. Random variables (A^i, $\overline{SR}$, ED and BW) were sampled from the distributions described in Table 1. The midline of the box represents the median, the box edges are the 25th and 75th percentiles, the whiskers are the 10th and 90th percentiles, and the points are the 5th and 95th percentiles. "Reg" denotes "regular" cigarettes having FTC tar content ⩾15 mg tar/cig, and "Lt" denotes "light" cigarettes having an FTC tar content of 6 to <15 mg tar/cig.

distributions (Table 3) were 0.6–1.2 times the corresponding values calculated from Djordjevic et al. reported in Table 2. All female median $ILCR_z^{i-MC}$ values are slightly greater than the corresponding male median $ILCR_z^{i-MC}$ values. This result is reasonable given that the Djordjevic et al. data for "regular" cigarettes result in median $ILCR_z^{NNN}$ and $ILCR_z^{NNK}$ values that are higher for female smokers than for male smokers (see Table 2). The fitted distributions for A^i and BW (Table 1) show that most of the female A^i distributions have slightly higher medians than their male counterparts (exceptions include BaP from "regular" cigarettes and NNK from "light" cigarettes), and BW distributions for females have lower medians; both of these differences contribute to the higher $ILCR_z^{i-MC}$ values for females.

In the following comparison of $ILCR_z^i$ with $ILCR_{CMD}^{obs\Sigma-lung}$ we focus on risks from NNK because median $ILCR_z^{NNK-MC}$ values were ~18× and 120× greater than the median $ILCR_z^{NNN-MC}$ and $ILCR_z^{BaP-MC}$ values, respectively. However, since $ILCR_z^{NNK-MC}$ predicts a risk corresponding to being diagnosed with any type of cancer from NNK exposure, we computed $ILCR_z^{NNK-lung}$ values (Table 4) for lung cancer risk alone by using $CSF^{NNK\text{-}lung}$ (=28 (mg/kg-day)$^{-1}$) instead of CSF^{NNK} (=49 (mg/kg-day)$^{-1}$). A more detailed discussion of NNK CSF values is provided in a California Environmental Protection Agency report (2001).

Stratified by $\overline{SR}$ ranges, Table 4 summarizes $ILCR_{CMD}^{obs\Sigma-lung}$ values from CPS-I and II, and median $ILCR_z^{NNK-lung}$ values from our MC simulations (values are reported per 100,000). For males, $ILCR_{CMD}^{obs\Sigma-lung}$ values from CPS-$I^{(6y\&12y)}$, ranged from 0.02 ($\overline{SR}$ = 1–9 cig/day) to 0.13 ($\overline{SR}$ = 40+ cig/day), and CPS-II^{6y} $ILCR_{CMD}^{obs\Sigma-lung}$ values of 0.10 and 0.14 were found for $\overline{SR}$ equal to 20 and 40 cig/day, respectively. Risks for females were much lower: CPS-$I^{(6y\&12y)}$ risks ranged from 0.0009 ($\overline{SR}$ = 1–9 cig/day) to 0.05 ($\overline{SR}$ = 21 to 39 and 40+ cig/day); and CPS-II^{6y} risks of 0.07 and 0.10 were found for $\overline{SR}$ = 20 and 40 cig/day, respectively.

Fig. 2 plots $ILCR_{CMD}^{obs\Sigma-lung}$ versus mid-range *z* values, where the mid-range *z* value is halfway between the lowest and highest *z* values calculated for each $\overline{SR}$ range and an ED range from 1 to 69 years of smoking. The lowest *z* value was calculated using the lowest $\overline{SR}$ of an $\overline{SR}$ range, and ED of 1 year for CPS-I^{12y} since a reported value of 0 would pertain to a non-smoker (lower bound ED = 30 years for CPS-I^{6y} and CPS-II^{6y}). Assuming that no smoker started before age five, the upper bound was calculated with the highest $\overline{SR}$ for an $\overline{SR}$ range and an ED of 69 years (upper bound ED = 50 years for CPS-I^{6y} and CPS-II^{6y}) because lifetime risks were computed for attained ages up to 74 years. For example, for $\overline{SR}$ = 1–9 cig/day and ED = 1–69 years of smoking, *z* ranges from 0.05 to 31 pack-years; the mid-range *z* value = 15.6. In Fig. 2, the relationship between log ILCR and log *z* appears linear for both $ILCR_{CMD}^{obs\Sigma-lung}$ and $ILCR_z^{NNK-lung}$. However, we did not statistically evaluate the relationship between log $ILCR_{CMD}^{obs\Sigma-lung}$ and log *z* because of uncertainty in the *z* values as depicted by the error bars.

We found median $ILCR_z^{NNK-lung}$ values determined by MC simulation to be one to two orders of magnitude lower than $ILCR_{CMD}^{obs\Sigma-lung}$ values. For smokers of "regular" cigarettes, median $ILCR_z^{NNK-lung}$ values compared to $ILCR_{CMD}^{obs\Sigma-lung}$ values from CPS-$I^{(6y\&12y)}$ and CPS-II^{6y} were lower for men by factors of 70–200, and for women by factors of 5–100 (Table 4). In women, the smaller differences between $ILCR_z^{NNK-lung}$ and $ILCR_{CMD}^{obs\Sigma-lung}$ arise because of much lower $ILCR_{CMD}^{obs\Sigma-lung}$ derived from CPS-I data. Compared to $ILCR_{CMD}^{obs\Sigma-lung}$ values from CPS-II^{6y} alone, median $ILCR_z^{NNK-lung}$ values for men are lower by factors of 200 ($\overline{SR}$ = 20 cig/day) and 100 ($\overline{SR}$ = 40+ cig/day); and median $ILCR_z^{NNK-lung}$ values for women are lower by factors of 100 ($\overline{SR}$ = 20 cig/day) and 60 ($\overline{SR}$ = 40+ cig/day). Since

Table 3
Summary statistics for incremental lifetime cancer risk (per 100,000) from 1,000 Monte Carlo simulations: mean ($\overline{ILCR}_z^{i-MC}$); standard deviation (σ); median (median$^{i\text{-MC}}$); 2.5th percentile and 97.5th percentile of the distribution; and ratios of Monte Carlo simulated $ILCR_z^{i-MC}$ mean and median values to Djordjevic et al. (2000) mean and median values for benzo[a]pyrene (BaP), *N*′-nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). CSF^i = cancer slope factor for carcinogen *i*.

	"Regular" cigarettes		"Light" cigarettes	
Toxicant	Male smokers	Female smokers	Male smokers	Female smokers
Benzo[a]pyrene (BaP); CSF^{BaP} = 3.9 (mg/kg-day)$^{-1}$				
$\overline{ILCR}_z^{BaP-MC}(\sigma)$	0.54 (0.54)	0.53 (0.53)	0.42 (0.48)	0.53 (0.46)
Median$^{BaP\text{-}MC}$	0.38	0.43	0.28	0.41
2.5th percentile	0.040	0.042	0.029	0.052
97.5th percentile	1.8	1.6	1.6	1.7
$\overline{ILCR}_z^{BaP-MC}/\overline{ILCR}_z^{BaP}$	0.7	0.8	0.6	1.0
Median$^{BaP\text{-}MC$/Median^{BaP}	0.8	1.0	0.7	1.1
N′-nitrosonornicotine (NNN); CSF^{NNN} = 1.4 (mg/kg-day)$^{-1}$				
$\overline{ILCR}_z^{NNN-MC}(\sigma)$	3.8 (3.4)	4.8 (4.2)	2.8 (2.8)	3.2 (3.1)
Median$^{NNN\text{-}M}$	3.0	3.7	2.0	2.3
2.5th percentile	0.23	0.45	0.18	0.27
97.5th percentile	12	16	10	12
$\overline{ILCR}_z^{NNN-MC}/\overline{ILCR}_z^{NNN}$	0.8	0.8	0.7	0.8
Median$^{NNN\text{-}MC$/Median^{NNN}	1.1	1.2	0.8	1.0
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK); CSF^{NNK} = 49 (mg/kg-day)$^{-1}$				
$\overline{ILCR}_z^{NNK-MC}(\sigma)$	73 (71)	87 (80)	58 (60)	71 (70)
Median$^{NNK\text{-}MC}$	53	66	38	50
2.5th percentile	5.3	5.8	3.9	4.2
97.5th percentile	242	311	239	246
$\overline{ILCR}_z^{NNK-MC}/\overline{ILCR}_z^{NNK}$	0.7	0.8	0.7	0.8
Median$^{NNK\text{-}MC$/Median^{NNK}	1.1	0.8	0.6	1.0

Table 4
Stratified by smoking rate, incremental lifetime cancer risks per 100,000 ($ILCR_{CMD}^{obs\Sigma-lung}$) calculated from American Cancer Society (ACS) Cancer Prevention Study (CPS) I and II (National Cancer Institute, 1997), and median $ILCR_z^{NNK-lung}$ values from Monte Carlo simulations per 100,000.

Average smoking rate (cig/day)	1–9	10–19	20	21–39	40+
ACS CPS-I $ILCR_{CMD}^{obs\Sigma-lung}$					
12-year follow-up[a,b]					
White male	1800	5100	7900	12,000	13,000
White female	95	750	2700	4800	4800
6-year follow-up[a,b]					
White male	–	–	6700	–	10,000
White female	–	–	1300	–	3300
ACS CPS-II *$ILCR_{CMD}^{obs\Sigma-lung}$*; 6-year follow-up[a,b]					
White male	–	–	10,000	–	14,000
White female	–	–	7000	–	9800
Monte Carlo simulation of incremental lifetime cancer risks for lung cancer from NNK[c] exposure ($ILCR_z^{NNK-lung}$)					
Male smokers of "regular" cigarettes[d]	15	30	48	55	140
Male smokers of "light" cigarettes[d]	12	23	24	38	76
Female smokers of "regular" cigarettes[d]	20	38	68	68	180
Female smokers of "light" cigarettes[d]	16	27	48	58	100

[a] Calculated using mortality data, and incidence to mortality ratios determined from SEER data 1973–2002 (SEER, 2006a,b): CPS-I males = 1.2 for 1973; CPS-I females = 1.4 for 1973; CPS-II males = 1.1 for 1988; and CPS-II females = 1.4 for 1988.

[b] 12-year follow-up lifetime risks based on attained ages 40–74; 6-year follow-up lifetime risks based on attained ages 50–74.

[c] NNK is 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; cancer slope factor = 28 (mg/kg-day)$^{-1}$ for lung cancer as an endpoint only (California Environmental Protection Agency, 2001).

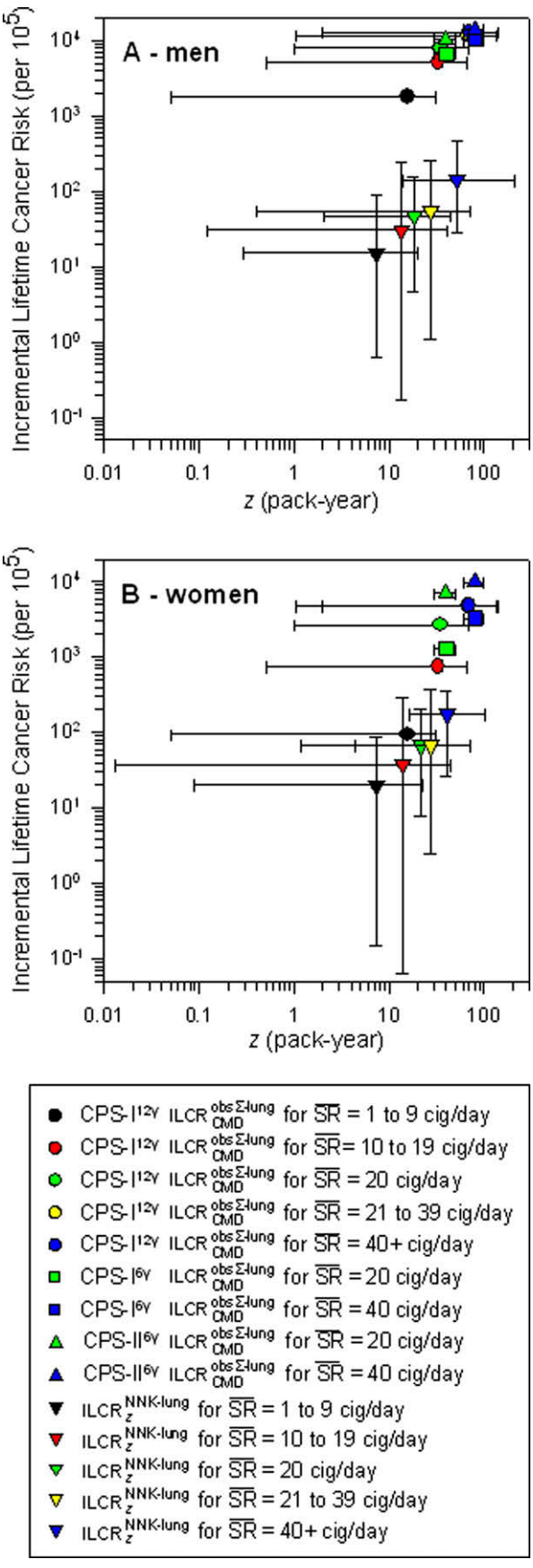
[d] Cigarette type determined from Federal Trade Commission tar content: "regular" ⩾15 mg tar/cig; and "light", 6 mg tar/cig to <15 mg tar.

CPS-I^{12y} ended in 1972, and "light" cigarettes were introduced in the 1970s, median $ILCR_z^{NNK-lung}$ for male and female smokers of "light" cigarettes were compared with only $ILCR_{CMD}^{obs\Sigma-lung}$ from CPS-II^{6y}. In men, $ILCR_z^{NNK-lung}$ values were lower than $ILCR_{CMD}^{obs\Sigma-lung}$ values by factors of 400 ($\overline{SR}$ = 20 cig/day) and 200 ($\overline{SR}$ = 40 cig/day); and in women the values differed by factors of 150 ($\overline{SR}$ = 20 cig/day) and 100 ($\overline{SR}$ = 40 cig/day).

For all $ILCR_{CMD}^{obs\Sigma-lung}$ values computed from CPS-I and II, values for men are higher than values for women in each $\overline{SR}$ range. The disparity is much greater for CPS-I$^{6y\&12y}$ where $ILCR_{CMD}^{obs\Sigma-lung}$ values for men are two to 20 times greater than values for women; for CPS-II^{6y}, $ILCR_{CMD}^{obs\Sigma-lung}$ values for men are ~1.5 times greater than values for women (see Section 4).

3.1. Distributions of z

Using a Kruskal–Wallis test, we found no statistically significant differences (p-value = 0.3) in the median z values of the four MC-simulated distributions of z used in calculating NNK risks, z values derived from Djordjevic et al. and z values derived from NHANES (Online Supplement Fig. S2). The Kruskal–Wallis test, however, will not detect all differences between the distributions, e.g., differences in variance (see below). Median z values from the MC simulations are approximately equal to the medians observed for subjects in Djordjevic et al. and NHANES (ratios range from 0.9 to 1.2). The NHANES z values in Fig. S2 support the low z values (below the 10th percentile) obtained through MC simulation, but



not observed in the Djordjevic et al. study subjects. However, the variances of the MC-simulated z-value distributions are smaller than the variances of z values from Djordjevic et al. and NHANES.

4. Discussion

The benefit of the MC method used here over deterministic approaches used in other studies (Vorhees and Dodson, 1999; Fowles and Dybing, 2003; Pankow et al., 2007) is the ability to account for variability in how people smoke cigarettes. By randomly sampling distributions for A^i, BW, $\overline{SR}$, and ED that represent values from real smokers, we obtained distributions of ILCR values that characterize carcinogen-specific risks in male or female smokers of "regular" or "light" cigarettes. Values of A^i under human smoking conditions were limited to measurements made by Djordjevic et al. (2000) because other data sets of comparable breadth and quality were not available. For example, in a recent study, Werley et al. (2008) measured emissions of 48 chemicals (including BaP, NNN, and NNK) in MCS of Marlboro Light which was machine-smoked under one human smoking condition protocol. However, these data cannot be used in our study directly because $\overline{SR}$, ED, and BW were not reported, and we are interested in evaluating a range of human smoking conditions not just one. In contrast, NHANES provided a much larger database of smokers for determining BW distributions for the MC simulations, and for evaluating our simulated distributions of z values.

Medians of the MC-simulated z-value distributions were consistent with Djordjevic et al. and NHANES, but the variances of the MC-simulated z-value distributions were smaller. Further examination of the empirical cumulative distribution functions (CDFs) for $\overline{SR}$ and ED reveals that CDFs of $\overline{SR}$ from the MC simulations, Djordjevic et al. and NHANES are all similar. And, ED CDFs from the MC simulations are similar to the ED CDF from Djordjevic et al. However, the MC-simulated ED distributions have lower variances than the NHANES ED distribution due to truncation of the normal distribution at an upper bound of 50 years of smoking determined from the Djordjevic et al. data. In contrast, NHANES data indicate an upper bound of 70 years, which is consistent with the upper limit on ED used to calculate $ILCR_{CMD}^{obs\Sigma-lung}$ values from CPS-I^{12y}. Since, $ILCR_z^i$ is directly proportional to z, the resulting variances of the $ILCR_z^{i-MC}$ distributions should be lower than the variances in epidemiologically derived $ILCR_{CMD}^{obs\Sigma-lung}$. Increasing the upper bound on the ED distribution would increase both the MC-simulated median z and median $ILCR_z^{NNK-lung}$ values resulting in a shift of all MC-simulated points upward and to the right in Fig. 2. Even with this adjustment, though, median $ILCR_z^{NNK-lung}$ values would remain approximately one to two orders of magnitude lower than $ILCR_{CMD}^{obs\Sigma-lung}$.

For Marlboro Light cigarettes machine-smoked under one human smoking condition, Werley et al. (2008) report emissions of BaP (10.1 ng/cig), NNN (146 ng/cig), and NNK (92.7 ng/cig). These emission values are 0.43–0.63 times lower than the median emission values measured by Djordjevic et al. (2000) for male and female smokers of "light" cigarettes, and used approximately 2 fewer puffs per cigarette and interpuff intervals about twice as

Fig. 2. Stratified by smoking rate ($\overline{SR}$) ranges, median incremental lifetime cancer risks from Monte Carlo simulation versus mid-range z values. ▽ = median $ILCR_z^{NNK-lung}$ for smokers of "regular" cigarettes; error bars mark the lower and upper bounds of the simulated values. $ILCR_{CMD}^{obs\Sigma-lung}$ computed from data for attained age up to 74 years and the sum of observed deaths over all exposure durations from 0 to 69 years: ○ = Cancer Prevention Study (CPS) I, 12-year follow-up; □ = CPS-I, 6-year follow-up; and Δ = CPS-II, 6-year follow-up. Results for: A—men; and B—women.

long as the mean values reported by Djordjevic et al. With all other parameters held constant (e.g., $\overline{SR}$, ED), a decrease in A^i will result in a proportional decrease in $ILCR_z^i$ given the linear dependence of $ILCR_z^i$ upon A^i.

We found CPS-I^{12y} $ILCR_{CMD}^{obs\Sigma-lung}$ values for males to range from 2- to 20-fold greater than the corresponding value for females; the largest fold-differences correspond to the two lowest $\overline{SR}$ ranges, namely 1–9 and 10–19 cig/day. In the two lowest $\overline{SR}$ ranges there were more PYO for women than men, whereas in the three higher $\overline{SR}$ ranges there were more PYO for men than women ($ILCR_{CMD}^{obs\Sigma-lung}$ for men are 2- to 3-fold greater than women). The gender difference in $ILCR_{CMD}^{obs\Sigma-lung}$ can be attributed to differences in excess mortality rates from CPS-I^{12y}, and possible causes of this have been of considerable interest. In Chapter 3 of Smoking and Tobacco Control Monograph 8 (National Cancer Institute, 1997), Burns et al. state:

> "*Part of the difference between white males and white females in relative and excess mortality is attributable to differences in duration of smoking between males and females of the same age, particularly among the older age groups. Males began to smoke cigarettes in large numbers in the early part of this century, whereas females initiated smoking during the late 1930's and 1940's* (*see Chapter 3*). *Female smokers in CPS-I also smoked fewer cigarettes per day than male smokers, contributing to their lower age-specific rate ratios.*"

It is also possible that the difference is due to a lower degree of smoke inhalation by women in CPS-I (Garfinkel and Stellman, 1988). The lower lung cancer risks observed for women in CPS-I compared to men are in contrast to more recent studies that indicate somewhat higher lung cancer risks for American women compared to men (Risch et al., 1993; Zang and Wynder, 1996; US Department of Health and Human Services, 2001; Belani et al., 2007), and comparable risks for men and women in both Germany and Italy (Kreuzer et al., 2000).

A challenge for the evaluation of cancer risk assessment methodology is obtaining human epidemiologic data, ideally a prospective study where exposures are tracked over the course of the study. For smoking, CPS-I and II are the best publicly available epidemiologic studies that provide data to calculate $ILCR_{CMD}^{obs\Sigma-lung}$ values. However, a limitation of comparing CPS-I and II data with $ILCR_z^i$ values computed for chemical emissions from cigarettes is the time frame over which these studies were conducted because of changes in cigarette design. We categorized cigarettes as "regular" or "light" based on FTC tar content, however, cigarettes available at the time CPS-I and II were conducted (1960–1972 and 1982–1988, respectively) may have had higher FTC tar content. Thus, MCS emissions may have contained different amounts of BaP, NNN, and NNK since positive correlations have been shown between BaP, NNN, and NNK emissions and FTC tar content (Borgerding et al., 2000). Based upon the regression equations in Borgerding et al., an increase in FTC tar content from 15 to 25 mg/cig would result in 40% more BaP, 17% more NNN, and 14% more NNK. These numbers suggest higher CPS-period cigarette carcinogen emissions than those measured by Djordjevic et al. (2000), which would result in a proportional increase in carcinogen-specific ILCR values, but it is inconclusive whether the increase can account for the large differences between risks based on chemical carcinogen emissions and the values derived from CPS-I and II.

There has been discussion in the literature of how epidemiologic data have been used in various phases of quantitative risk assessment (Shore et al., 1992; Hertz-Picciotto, 1995; Wartenberg and Simon, 1995; Samet et al., 1998; Goldman, 2001), and a few studies have compared risks based on human dose–response data (primarily from occupational exposures) with risks computed from animal bioassay dose–response data (Allen et al., 1988; Hertz-Picciotto et al., 1988; Hertz-Picciotto and Hu, 1994). For 23 chemicals, Allen et al. (1988) compared the daily doses (mg/kg-day) that would cause cancer deaths in 25% of the exposed individuals derived from human epidemiologic studies and animal bioassay studies. They concluded that animal bioassay data were reasonable for quantifying human risks. For the risk of contact-site tumors from ethylene dibromide, Hertz-Picciotto et al. (1988) found excess risks computed from animal bioassay data to be consistent with human data. However, Hertz-Picciotto and Hu (1994) found that smoking-induced lung cancer risk attributable to cadmium (Cd) in MCS ranged from 13% to 18% of lung cancer risks derived from two different epidemiologic studies (Kahn, 1966; Mattson et al., 1987), but concluded that this overestimated the risks of Cd in MCS given the large number of known carcinogens in MCS.

The present study differs from previous work (Allen et al., 1988; Hertz-Picciotto et al., 1988; Hertz-Picciotto and Hu, 1994) in that CSF^i values derived from animal bioassay data were used to compute ILCR values for a range of human exposure scenarios and MCS carcinogen emissions measured under human smoking conditions, then the ILCR values were compared to lifetime risks derived from CPS-I and II. The best available CSF^i values were used, but it should be noted that for NNK, CSF^{NNK} values (e.g., for lung cancer or all cancer endpoints) were derived from animals exposed to NNK in drinking water rather than by inhalation (California Environmental Protection Agency, 2001). This study shows that median $ILCR_z^{NNK-lung}$ values for male smokers of "regular" or "light" cigarettes explain only 0.2–1% of the lung cancer risk in men derived from CPS-I and II; for female smokers median $ILCR_z^{NNK-lung}$ values explain 0.7–21% of the risks derived from CPS-I and II. For females, if CPS-I $ILCR_{CMD}^{obs\Sigma-lung}$ values are excluded because the female values are much lower than the male values, median $ILCR_z^{NNK-lung}$ values explain 0.7–2% of the epidemiologically derived risk. Accounting for higher carcinogen emissions in CPS-period cigarettes and inclusion of other MCS carcinogens to compute a cumulative risk following an additive risk model (US Environmental Protection Agency, 1986; Krewski and Thomas, 1992) as done by Pankow et al. (2007) would reduce the difference between risks based on chemical carcinogen emissions and the values derived from CPS-I and II. However, results from this study indicate that for men, this would require the equivalent of ~100 lung carcinogens having the same magnitude of risk as NNK out of the 69 known MCS carcinogens. Moreover, an examination of ILCR values calculated for 13 carcinogens by Pankow et al. (2007) and 30 carcinogens by Vorhees and Dodson (1999) (all cancer endpoints included), yields at most nine carcinogens (i.e., in alphabetical order, 1,3-butadiene, acetaldehyde, acrylonitrile, arsenic, benzene, cadmium, formaldehyde, NNN and quinoline) with risk values of the same order of magnitude or within one order of magnitude below the NNK risk (see Pankow et al. (2007) Supplementary Fig. S1). These findings suggest that MCS may cause a much higher incidence of lung cancer than can be predicted from current risk assessment methods on a carcinogen-specific basis with available toxicity data and emission data measured under human smoking conditions. This conclusion stems from the fact that any given sample of cigarette smoke is a complex chemical mixture that contains not only complete carcinogens such as NNK, NNN, and BaP, but also many chemicals that are co-carcinogens, cancer initiators, or cancer promoters (Loeb et al., 1984; Preston-Martin et al., 1991; Hoffmann and Hoffmann, 2001; Lemjabbar et al., 2003; Hazelton et al., 2005). It is therefore quite possible that complete removal of NNK, NNN, and BaP from mainstream smoke of PREP products would bring little or no reduction in cancer risks due to smoking, which is consistent with the views of Loeb et al. (1984) and Pankow et al. (2007). Furthermore, whether an individual develops lung cancer depends upon individual susceptibility due to genetic, behavioral and

environmental factors (Belani et al., 2007; Engels et al., 2007). All of these effects are subject to amplification when yet other chemicals impair normal lung clearing functions so that carcinogens and toxicants can reside in the respiratory tract for relatively longer periods of time. Thus, for the protection of public health, it is more important to reduce smoking than to create cigarette products that attempt to reduce risks from smoking by removing selected chemicals from tobacco smoke.

The assessment of cancer risk from exposure to complex chemical mixtures such as MCS, requires a risk assessment approach that accounts for risk contributions from chemicals that are not complete carcinogens such as initiators and promoters, or combinations of such chemicals. Biologically based, multistage cancer models (Ellwein and Cohen, 1992; Moolgavkar and Luebeck, 1995) can simulate tumor probabilities from exposure to complete carcinogens, and combinations of initiators and promoters, but as a predictive tool such models require more data (e.g., the probabilities that cells will undergo mutations, cell proliferation, birth and death rates as functions of the carcinogen(s) of interest, etc.) than the ILCR approach used here. Thus, additional studies are needed to measure MCS chemical emissions, and to assess the toxicity and mechanisms of action of MCS chemicals. Furthermore, as with other complex chemical mixtures to which humans are exposed, more research is needed to develop better risk assessment methods and models that account for the biological complexities of smoking-induced cancers.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yrtph.2009.06.007.

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