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Biomonitoring of Smoke Constituents

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Exposure to 4-Aminobiphenyl and 4-Aminobiphenyl hemoglobin Adduct Levels in Non-smokers and Smokers‡

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‡ Schorp M.K., Leyden D.E., 2010. Exposure to 4-Aminobiphenyl and 4-Aminobiphenyl hemoglobin Adduct Levels in Non-smokers and Smokers. Inhalation Toxicology, 22; 725-737

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Objective

- 4-Aminobiphenyl (4-ABP) is a known human bladder carcinogen, present in both mainstream and sidestream cigarette smoke. Active smokers exhibit a several-fold (3-8 times) elevation in 4-aminobiphenyl hemoglobin (4–ABP–Hb) adduct levels compared to non-smokers

- Some publications have suggested that 4–ABP hemoglobin (4–ABP–Hb) adduct levels in non-smokers are a result of exposure to environmental tobacco smoke (ETS), whereas others could not confirm these observations

- Although it is clear that 4–ABP–Hb adduct levels are higher in smokers than non-smokers, **the mixed results question whether the contribution of ETS as a source of 4–ABP in non-smokers can be quantified reliably in field studies**

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Outline

- Part 1: 4-ABP-Hb levels in Non-smokers
  - 4-ABP levels in ETS
  - 4-ABP levels in indoor air in workplaces, hospitality, and home environments
  - Approach to estimate exposure and uptake of 4-ABP
  - Monte Carlo simulation of 4-ABP adduct levels
- Part 2: 4-ABP-Hb adduct levels in Smokers
- Conclusions

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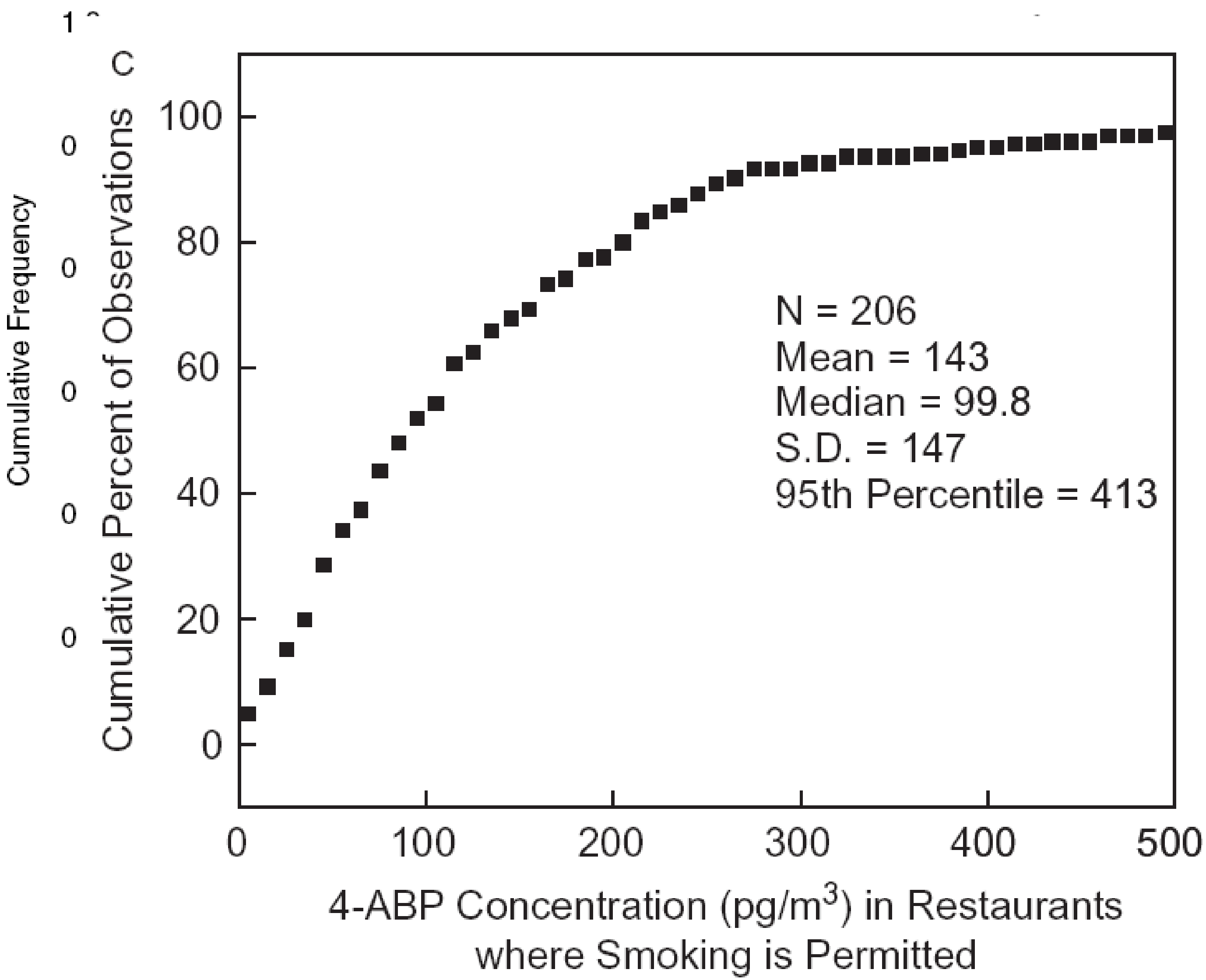
Part 1: 4-ABP-Hb levels in Non-smokers

Step 1: Determine 4-ABP/ETS-RSP ratio

- Analytical measurement issues for 4-ABP in indoor air suggest the need for a surrogate constituent such as respirable suspended particles (RSP)
- Many population-based data are available for RSP attributable to ETS (ETS-RSP) in indoor environments (e.g., workplace, home, hospitality)
- Few data are available on 4-ABP levels (pg/m^3) in indoor environments.
- If the 4-ABP/ETS-RSP ratio is determined, then the ETS-RSP data (µg/m^3) can be used to estimate 4-ABP levels from ETS-RSP in indoor air
- Mean value of 4-ABP/ETS-RSP ratio $(1.15 \pm 0.15) \times 10^{-6}$ was calculated from Tricker *et al.* 2009
- Cumulative distributions of 4-ABP indoor levels can therefore be calculated from the distribution of ETS-RSP levels

Tricker A.T., Schorp M.K., Urban H-J., *et al*. 2009. Inhal Toxicolol, 21; 61-77

Example - 4-ABP levels in restaurants calculated from 4-ABP/ETS-RSP ratio



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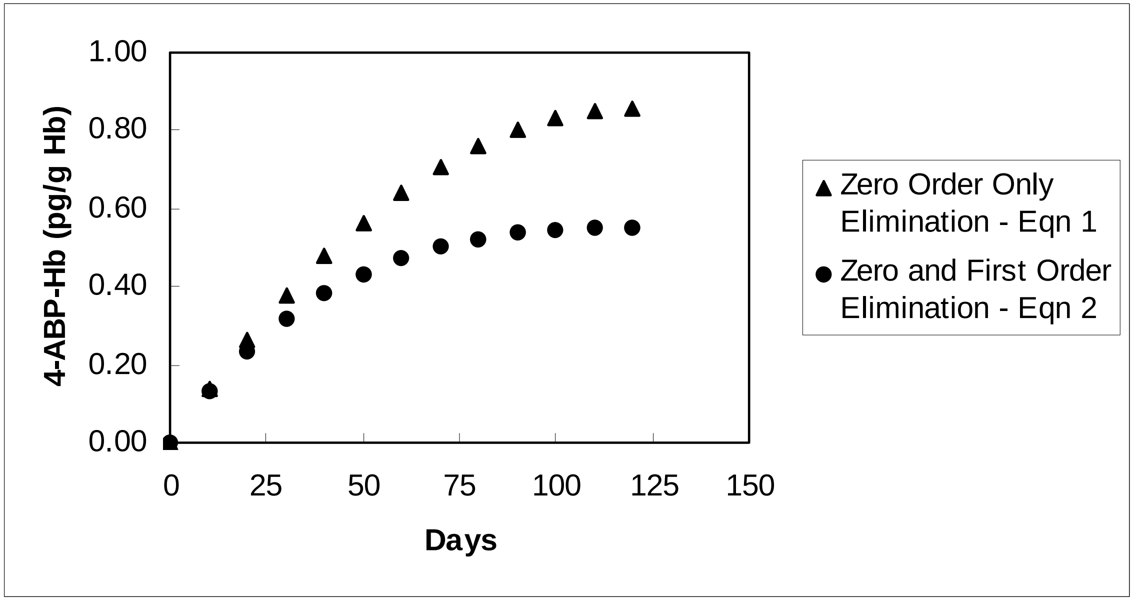
Step 2: Toxicokinetics



A_{ss} steady state adduct levels
A_c daily increment in adduct concentration
t_{er} erythrocyte lifetime
k first order rate constant

Chronic exposure time-dependence of 4–ABP–Hb adduct levels (A_{ss}) with two models (see below) of elimination and the following parameter assumptions: A_c = 0.14 pg/g Hb d-1 (Sabbioni, 1992) (150 pg/d 4-ABP, t_{er} = 120 d, k = 1.24 x 10-2 d-1, 8% conversion to adduct)

Zero Order

$$A_{ss} = A_{t_{er}} = \frac{1}{2} \bullet A_c \bullet t_{er}$$ Eqn. 1

Zero and First Order

$$A_{ss} = A_{t\,er} = \frac{A_c}{k}\left(1 - \frac{1 - e^{-kt_{er}}}{kt_{er}}\right)$$ Eqn. 2

Sabbioni G. 1992. Hemoglobin binding of monocyclic aromatic amines: molecular dosimetry and quantitative structure activity relationship for the N-oxidation. Chem-Biol Interactions, 81; 91-117.

Step 3: Estimation of 4-ABP uptake and 4-ABP-Hb adduct formation

From experimental RSP values and the 4-APB/RSP ratio, one may estimate the 4-ABP concentrations in smoking environments (e.g., 32.5 pg/m^3) may be used along with breathing rates (e.g., 0.83 m^3/h), particle deposition fraction (e.g., 0.2), and exposure time (e.g., 15h/day) to obtain a point estimate for the 4-ABP dose from ETS exposure (81 pg/d):

$$32.5\frac{pg}{m^3}\bullet 0.83\frac{m^3}{h}\bullet 0.2\bullet 15\frac{h}{d}=81\frac{pg}{d}$$

Eqn. 3

A point estimate for the formation of 4-ABP-Hb adduct levels (0.46 pg/g Hb) from the exposure above can be calculated, using adduct formation efficiency (e.g., 8%), hemoglobin mass of adult man (e.g., 840 g), and erythrocyte halftime (e.g., 60 days):

$$\left(81\ pg/d\bullet 0.08 \Big/ 840\ g\ Hb\right)\bullet\frac{120}{2}d=0.46\frac{pg}{g\ Hb}$$

Eqn. 4

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Step 4: Monte Carlo Simulation - Parameters used

Parameter	Mean	SD(±)	LL*	UL*	Distribution Type*
RSP Concentration from 16-Cities Study (μg/m³)					
Smoking Homes	41.16	44.78	0	517	LN
Smoking Workplaces	44.4	72.3	0	930	LN
ETS-RSP Concentration in Restaurants (μg/m³)	131	140	0	1035	LN
4-ABP/ETS-RSP Ratio	$1.15x10^{-6}$	$1.5x10^{-7}$	$9.0x10^{-7}$	$1.43x10^{-6}$	N
4-ABP Absorption Efficiency (Particle Deposition)	0.2	0.13	0.03	0.76	N
Respiration Rate (m³/h)					
Home	0.83	1.0	0.4	1.4	LN
Workplace	1.2	0.6	0.4	1.4	LN
Restaurants	1.2	0.6	0.4	1.4	LN
Duration of Exposure (h/day)					
Home	15	3	2	24	N
Workplace	8	2	2	12	N
Restaurant	8	2	0	16	N
4-ABP-Hb formation (%)	8.00%	2.00%	3.00%	11.00%	
Body Mass for Adult Male (GM and GSD)	76.8	1.18	-	-	LN

*LL = Lower Limit; UL = Upper Limit; N = normal; LN = lognormal

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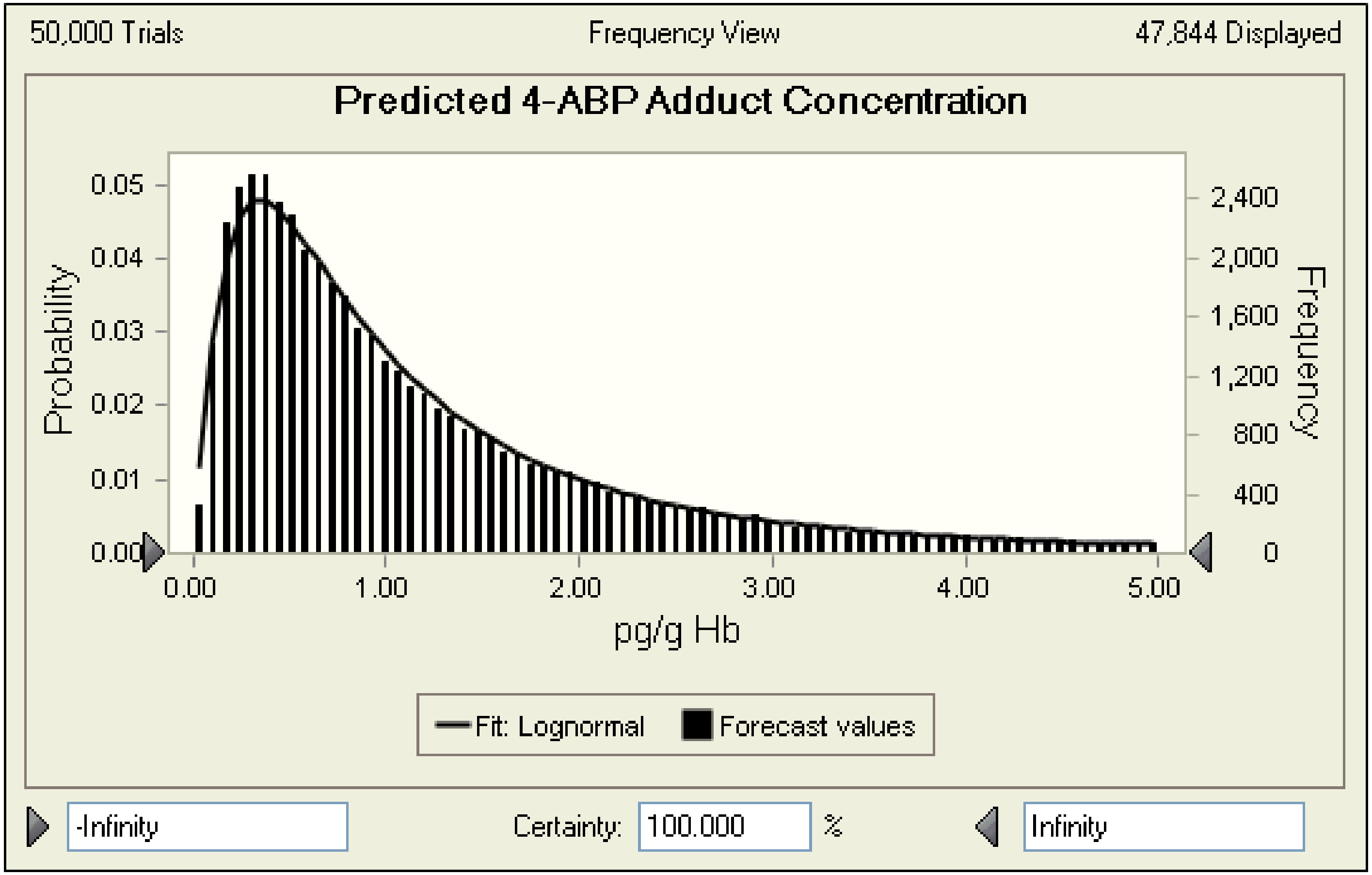
Step 4: Monte Carlo Simulation - Hypothetical population



Monte Carlo simulation of estimated 4-ABP-Hb adduct levels (pg/g Hb) for employees in restaurants **using experimental ETS-RSP Data. Mean: 1.44, median: 0.87, standard deviation: 1.79 pg/g Hb**

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Step 4: Literature Data and Monte Carlo Simulation

Source of Data	Mean 4–ABP–Hb (pg/g Hb)	Median 4–ABP–Hb (pg/g Hb)	SD 4–ABP–Hb (pg/g Hb)	95^{th} %ile
Statistically summarized values reported in literature for non-smokers	35	28	± 25	NA
Estimated to arise from ETS exposure by the use of experimental RSP Data in **homes** where smoking occurs and a 4-ABP/RSP ratio of 1.15×10^{-6} (Jenkins et al., 1996)	0.62	0.33	± 0.93	2.12
Estimated to arise from ETS exposure by the use of experimental RSP Data in **workplaces** where smoking occurs and a 4-ABP/ETS-RSP ratio of 1.15×10^{-6} (Jenkins et al., 1996)	0.37	0.23	± 0.44	1.17
Estimated to arise from ETS exposure by the use of experimental ETS-RSP Data from **restaurants** where smoking is permitted and a 4-ABP/ETS-RSP ratio of 1.15×10^{-6} (Bohanon Jr. et al., 2003)	1.44	0.87	± 1.79	4.63

Jenkins R.A., *et al.*,1996. Exposure to environmental tobacco smoke in sixteen cities in the United States as determined by personal breathing zone air sampling. J. Expo Anal Environ Epidemiol, 6; 473-502.

Bohanon H., *et al.*, 2003. J Expo Anal Environ Epidemiol,13; 378–392

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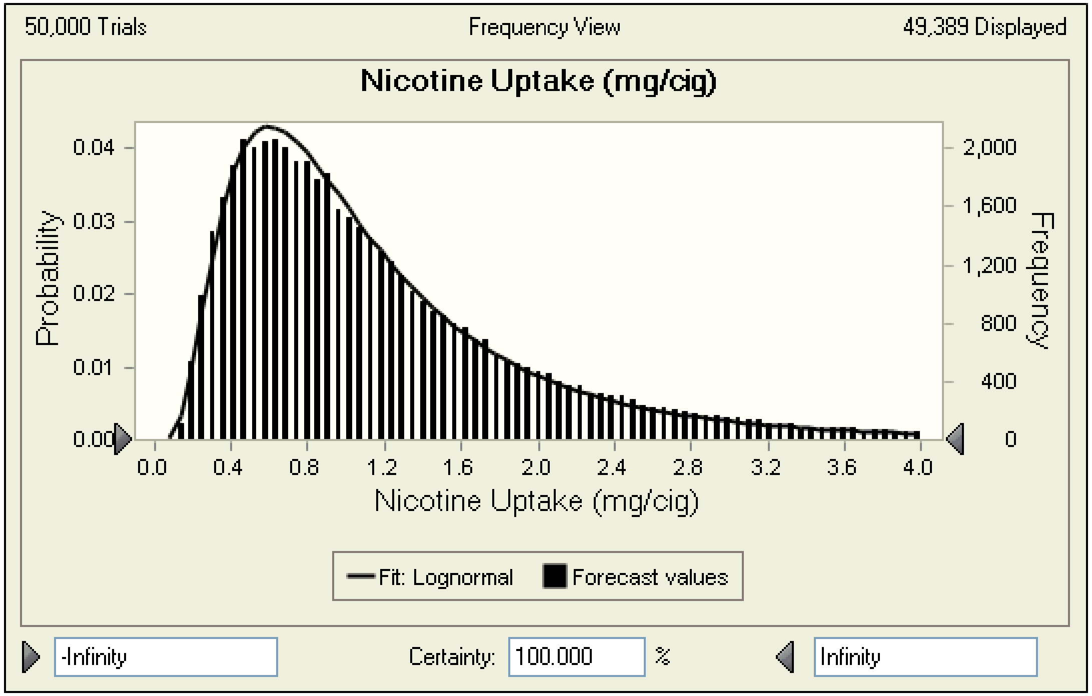
Part 2: 4-ABP-Hb levels in Smokers

Step 1: Nicotine uptake distribution

Constituent to nicotine ratios across the various smoking behaviors have been shown to be relatively constant; thus, the determination of nicotine uptake can be used to estimate the uptake of other smoke constituents (Urban and Schorp, 2006)



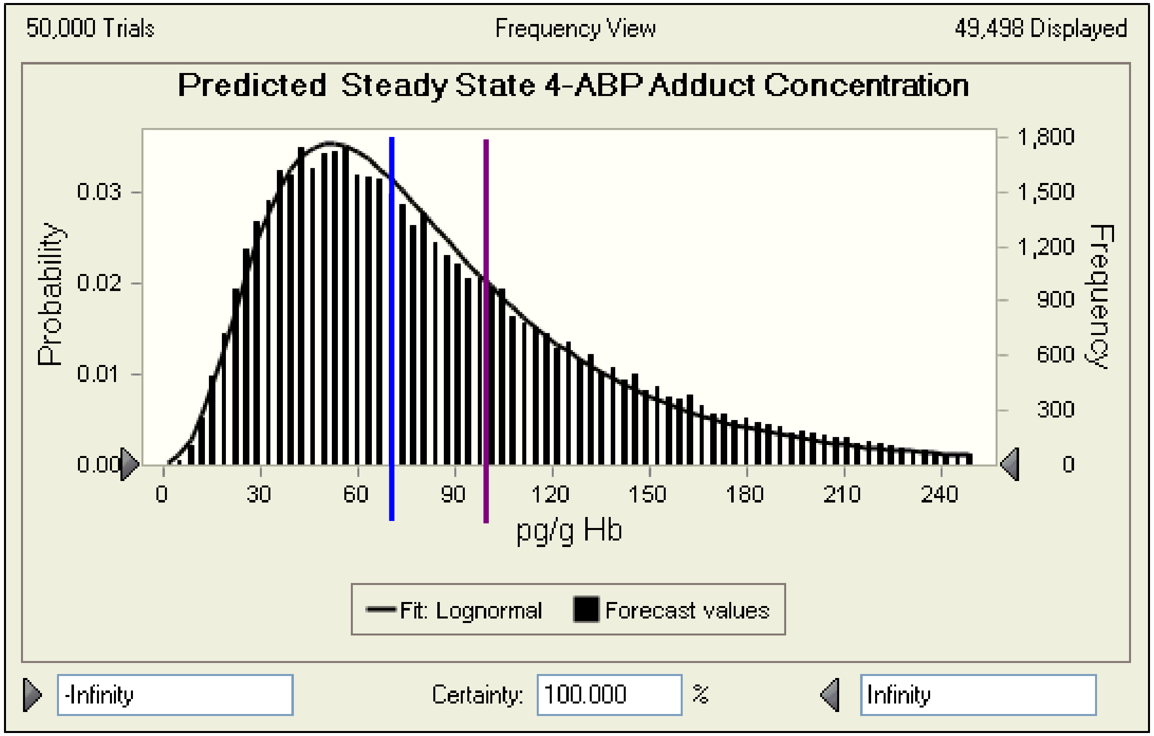
Distribution of nicotine uptake per cigarette (median: 0.98 mg/cig, mean: 1.45 mg/cig) obtained by Monte Carlo simulation using nicotine biomonitoring data for a population of predominantly American-blended cigarette smokers (Scherer et al., 2007)

Urban H-J, Schorp M., 2006. Nicotine bridging: A new method to extend smoke constituents biomarker measurements from clinical studies to other mainstream smoke constituents. (Abstract, poster). *Society for Risk Analysis Annual Meeting, December 4-6, 2006.* Baltimore, MD, USA.

Scherer G., *et al.* 2007. Relationship between machine-derived smoke yields and biomarkers in cigarette smokers in Germany. Regul Toxicol Pharmacol, 47**,** 171-183.

Step 2: Monte Carlo simulation of 4–ABP–Hb adducts in smokers

Using mean, SD, LL, UL for 4–ABP/nicotine ratio in mainstream smoke, particle retention, particle retention factor and the factor for conversion of 4–ABP to 4–ABP–Hb adducts, a Monte Carlo simulation of the nicotine uptake distribution is applied to obtain the distribution of steady-state levels of 4–ABP–Hb adducts in smokers



Distribution of steady state 4-ABP-Hb adduct level (pg/g Hb):

Predicted - median: 73 pg/g Hb (blue)

Statistically summarized from the literature – median 107 pg/g Hb (violet)

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Conclusions

- Based on our toxicokinetic model, 4–ABP–Hb adduct levels from ETS exposure account for approximately 1% to 4% of the median levels reported for non-smokers, explaining, in part, contradictory literature data on 4-ABP-Hb adduct levels in non-smokers

- Calculated 4–ABP–Hb adduct levels in smokers based on estimates of 4–ABP dose are in good agreement with the reported 4–ABP–Hb adduct levels in smokers, in part confirming the validity of the model

- The known health effects of ETS are neither confirmed nor challenged and our conclusions are limited to the determination that ETS is not a major source of 4-ABP-Hb adduct levels in non-smoking adults exposed to ETS

THANK YOU

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Backup

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Literature Data and Monte Carlo Simulation - Smoker

Source of Data	Mean 4–ABP–Hb (pg/g Hb)	Median 4–ABP–Hb (pg/g Hb)	SD 4–ABP–Hb (pg/g Hb)	95^{th} %ile
Statistically summarized values reported in literature for smokers	131	107	±102	NA
Predicted based on smoker exposure to cigarette smoke using 4-ABP/nicotine ratios (Counts et al., 2005) and nicotine uptake distributions (Scherer et al., 2007)	86	73	±53	185

Counts M.E., *et al.*, 2005. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regul Toxicol Pharmacol, 41; 185-227.

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