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Risk Assessment for diacetyl airborne exposures based on human studies: microwave popcorn workers

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Introduction

NIOSH did 6 HHEs in MW popcorn plant populations

-> 4 investigated -> 3 analyzed -> 1 basis for risk assessment

Cross-sectional designs: all but one HHEs did survey at one point in time; plant used for RA did 8 in surveys over 32 months

Primary plant: ~360 active employees participated in 1 or more surveys

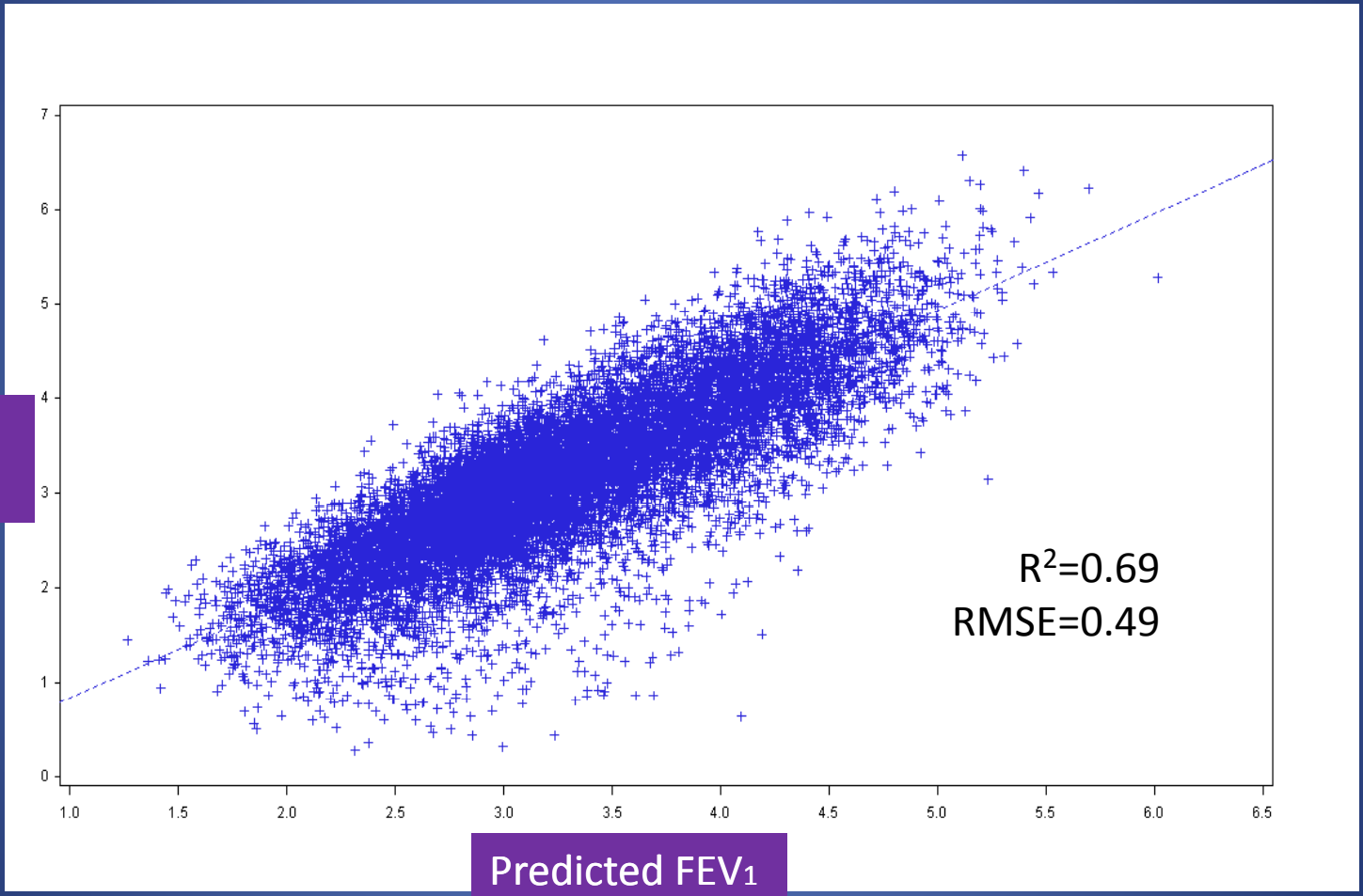
Two approaches: 1) loss of breathing capacity in surveyed population
2) onset of cases of pulmonary impairment

Diacetyl air-sampling results (corrected) at four HHE study sites in major process areas

Personal Samples

	Mixing		Production		Quality Control		Maintenance	
Site	n	Mean	n	Mean	n	Mean	n	Mean
N	1	0.79	7	0.740	2	0.250	2	0.160
K	5	0.31	7	0.040	3	0.003	3	0.020
L	10	1.15	36	0.028	5	0.034	6	0.014
G	25	2.36	112	0.490	20	0.370	17	0.080

Inherent variability of FEV_1 as observed in NHANES III population



Regression models for percent of predicted FEV_1 comparing diacetyl exposure metrics at Site G

	R^2	Intercept	*t*-statistic (1df) for Exposure Metric	*P* value
Avg(DA)	0.128	94.99	2.41	0.0167
$Cum(DA^{2.0})$	0.142	94.62	3.41	0.0007
$(Cum(DA))^{2.0}$	0.148	94.76	3.76	0.0002
Duration	0.161	97.17	4.43	9×10^{-6}
Cum(DA)	0.169	95.95	4.83	10^{-6}
$Cum(DA^{0.5})$	0.172	96.38	4.95	7×10^{-7}
$(Cum(DA))^{0.5}$	0.174	97.34	5.04	4×10^{-7}
$(Cum(DA^{0.5}))^{0.5}$	0.176	98.25	5.16	2×10^{-7}

Cum(DA) = cumulative exposure = Σ_i (DA) over time

Full regression models of percent of predicted FEV_1 for selected DA exposure metrics at Site G

	Cum(DA)		$(Cum(DA))^{0.5}$		$Cum(DA^{0.5})$	
	$R^2 = 0.169$		$R^2 = 0.174$		$R^2 = 0.172$	
	β	*P*	β	*P*	β	*P*
intercept	95.95	—	97.34	—	96.38	—
female	−0.386	0.82	0.092	0.96	−0.306	0.86
hispanic	1.99	0.40	1.42	0.55	1.70	0.47
black	8.58	0.45	7.78	0.49	8.30	0.46
smoke_ever	7.29	0.0020	6.86	0.0038	6.88	0.004
packyrs	−0.571	0.0008	−0.562	0.0009	−0.560	0.0009
packyr2	0.0024	0.36	0.0024	0.34	0.0025	0.32
DA exposure	−0.500	10^{-6}	−2.77	4×10^{-7}	−0.843	7×10^{-7}

Regression models for percent of predicted FEV_1 at three HHE study sites comparing diacetyl exposure metrics

	Cum(DA)			$(Cum(DA))^{0.5}$		
Site	β	R^2	P	β	R^2	P
K	−7.77	0.322	$< 10^{-7}$	−14.3	0.286	10^{-6}
L	−3.56	0.138	0.0012	−9.15	0.146	0.0004
G	−0.50	0.169	10^{-6}	−2.77	0.174	$< 10^{-6}$

Regression models for FEV_1 /FVC at three HHE study sites comparing diacetyl exposure metrics

	Cum(DA)			$(Cum(DA))^{0.5}$		
Site	β	R^2	P	β	R^2	P
K	−4.30	0.449	$< 10^{-7}$	−8.24	0.420	$< 10^{-7}$
L	−2.16	0.213	$< 10^{-5}$	−5.26	0.212	$< 10^{-5}$
G	−0.16	0.342	0.0024	−0.98	0.346	0.0007

Two definitions of case for onset of pulmonary impairment

1) FEV_1 < Lower Limit of Normal (LLofN) - defined from NHANES equations.

2) FEV_1 < LLofN **and** FEV_1/FVC < LLofN

Date of onset defined:

average date when continuing symptoms began (from questionnaire)

non-symptomatic cases excluded

Incidence of new cases (definition 2: FEV_1 and FEV_1/FVC < LLofN) in Poisson regression with log-linear models

Model	Metric	Effect Estimate	RR 5yr @ 2 ppm	Δ-2lnL	Wald *P*
1	Duration	-0.085	-	0.0	0.23
2	Cum(DA)	0.012	-	-	0.60
3	Duration	-0.300			0.023
	Cum(DA)	0.090	2.46	5.31	0.16
4	Duration	-0.555			0.036
	$Cum(DA^{0.5})$	0.316	9.37	5.50	0.041
5	Duration	-0.411			0.0085
	$(Cum(DA))^{0.5}$	0.804	12.7	8.76	0.005
6	Duration	-0.088			0.24
	Avg(DA)	0.468	2.55	8.75	0.001

Predicted rate ratios relative to a fixed baseline rate

Case definition 2: Rate Ratio (relative to baseline: 0.0046)

Duration (yrs)	Cumulative Diacetyl Exposure (ppm-yrs)					
	< 0.5	0.5<2.0	2.0<3.0	3.0<5.0	≥ 5.0	All
< 0.5	5.39	6.54	1.91	1.15	—	5.67
0.5 <1.0	4.39	6.22	6.57	7.70	5.39	5.59
1.0<2.0	4.26	3.72	7.00	7.63	6.98	6.22
2.0<4.0	2.54	4.43	4.70	5.61	7.74	6.63
≥ 4.0	0.83	0.85	3.15	1.57	5.11	4.33
All	4.22	4.89	5.85	6.17	5.85	5.35

Linear relative-rate model to describe incidence of cases with apparent declining susceptibility or response to exposure

$$\text{rate} = \{\exp(\alpha+\beta\text{smoker}+\gamma\text{sex}+\delta(\text{age}-40)+\varepsilon(\text{age}-40)^2)\} \times \{1+\theta\text{packyrs}+\sigma\mathbf{HRX}+\mu\text{cumDA}\}$$

HRX = $[DA]^2\exp(-0.693\text{dur}/\mathbf{2.0})$ – for half-life = 2.0 yr

2 yr half-life produces better fit than 1 yr

$[DA]^2$ fits better than [DA]

Incidence of new cases (defn2: FEV_1, $FEV_1/FVC < LLofN$)
Poisson regression with linear relative-rate model

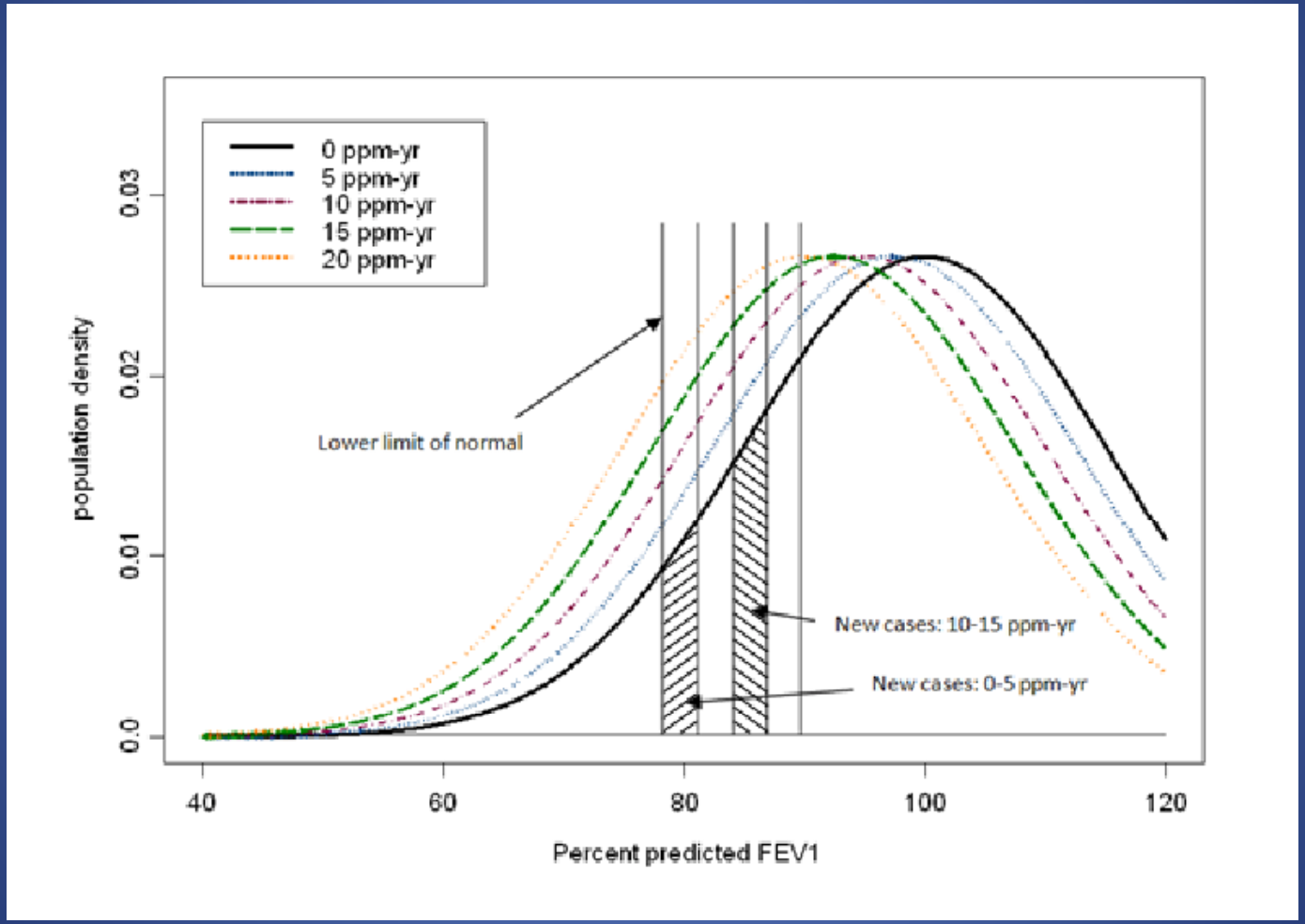
Parameter	Estimate	RR	LRT	*P* value
intercept	−15.5			
smoke_ever	−0.68	0.51		
Ind:female	0.97	2.63		
age-40	0.041	1.04		
$(age-40)^2$	−0.002	0.998		
packyrs	17.7	18.7		
cum(DA)	12.3	13.3	2.19	0.07
HRX (t-half =2 yr)	69.8	70.8	7.78	0.0026

Rate = $\{\exp(\alpha + \beta smoker + \gamma sex + \delta(age-40) + \varepsilon(age-40)^2)\}\{1 + \theta packyrs + \sigma HRX + \mu cumDA\}$

RR - @ 1 pack-yr, 1 ppm at day 1 (HRX), 1 ppm-yr (cum(DA)); p value: one-tailed

HRX = $[DA]^2 \exp(-0.693 dur/2)$ – for half-life = 2.0 yr

BMD paradigm: assumes uniform response – susceptibility – and known distribution



Benchmark dose for pulmonary impairment based on cum(DA) metric and 45 yr work-life

DA (ppm)	cum. exp. (ppm-yrs)	Model-predicted ppFEV$_1$	Percent of predicted FEV$_1$ Excess Prevalence per 1000 < 60% of predicted	Percent of predicted FEV$_1$ Excess Prevalence per 1000 < 5th percentile
1	45.0	77.5	126.7	366.8
0.5	22.5	88.8	27.9	126.7
0.2	9.00	95.5	6.4	37.2
0.1	4.50	97.8	2.7	16.6
0.05	2.25	98.9	1.2	7.8
0.02	0.90	99.6	0.5	3.0
0.01	0.45	99.8	0.2	1.5
0.005	0.225	99.89	0.1	0.7
0.002	0.090	99.96	0.0	0.3
0.001	0.045	99.98	0.0	0.1
0.0005	0.0225	99.99	0.0	0.1
0.0002	0.0090	100.00	0.0	0.0

Empirical benchmark doses for FEV_1 and FEV_1/FVC for 45 yr worklife using NHANES population

	Excess prevalence (per 1000)	
DA (ppm)	FEV_1	FEV_1/FVC
1	532.5	220.5
0.5	202.9	82.4
0.2	58.7	27.4
0.1	25.7	12.1
0.05	12.3	6.8
0.02	4.8	3.2
0.01	2.5	2.1
0.005	1.3	1.0
0.004	0.4	0.4
0.003	0.2	0.3
0.002	0.2	0.2
0.001	0.1	0.1
0.0005	0.1	0.1

Excess lifetime risk for becoming a case (definition 2) based on life-table (BEIR IV) analysis for 45 yr work-life

DA (ppm)	per 1000
1	248.8
0.5	140.7
0.2	60.8
0.1	31.2
0.05	15.8
0.02	6.4
0.01	3.2
0.005	1.6
0.002	0.6
0.001	0.3
0.0005	0.2
0.0002	0.1
0.0001	0.0

Excess lifetime risk of mortality associated with declining FEV_1

- Published literature indicates 1% loss of FEV_1 is associated with ~ 1.5% increase in mortality rate independent of other risk factors such as age, gender, race, BMI.

- This is not specific to bronchiolitis obliterans, rather a generic effect.

- Using exposure response for FEV_1 based on cum(DA), estimate excess mortality with lifetable method:

DA (ppm)	Per 1000
1.0	221.6
0.5	121.1
0.2	51.2
0.1	26.1
0.05	13.2
0.02	5.30
0.01	2.65
0.005	1.33
0.002	0.53
0.001	0.27
0.0005	0.13
0.0002	0.05

Summary of risk assessment findings in range 0.05 – 0.001 ppm diacetyl

DA		Method (per 1000)			
		BMD Excess Prevalence		Life-table Excess Lifetime Risk	
		Impairment			
ppm	ppb	FEV_1 (<LLofN)	FEV_1/FVC (<LLofN)	Case onset (definition 2)	Mortality
0.05	50	12.3	6.8	15.8	13.2
0.02	20	4.8	3.2	6.4	5.3
0.01	10	2.5	2.1	3.2	2.7
0.005	5	1.3	1.0	1.6	1.3
0.004	4	1.1	0.8	1.3	1.1
0.003	3	0.6	0.6	1.0	0.8
0.002	2	0.4	0.4	0.6	0.5
0.001	1	0.2	0.3	0.3	0.3

Summary of risk assessment findings by level of lifetime risk for diacetyl

	Method			
	BMD Excess Prevalence (ppb)		Life-table Excess Lifetime Risk (ppb)	
	Impairment			
Lifetime Risk	FEV_1 (LLofN)	FEV_1/FVC (LLofN)	Case onset (definition 2)	Mortality
1/10	300	600	300	400
1/100	40	80	30	40
1/1000	4	5	3	4
1/10000	0.4	0.5	0.2	0.4
1/100000	0.04	0.05	0.02	0.04

Issues addressed in NIOSH risk assessment for diacetyl

- Exposure assessment: unusually extensive with declining levels described
- Definition of impairment: analyses of outcomes that would encompass both obstructive and restrictive disease produced concordant estimates of risk as did three risk assessment methods
- Cross-sectional study limitations: affected workers leaving employment likely has resulted in under-estimation of exposure response, as did exclusion of asymptomatic cases in the incidence analysis
- Apparent unknown variability in susceptibility required an ad hoc statistical model specification which accommodated higher risk in a declining subpopulation, or, generally declining susceptibility with exposure duration

…Issues addressed

- 45 yr exposure in a single hypothetical population would under-estimate the impact of variable susceptibility (survivor bias)

- Low dose extrapolation: career-average DA exposures at Site G were below 0.01 ppm in 13% of workers; proposed REL is only factor of 2 below 0.01 ppm.