The ACGIH BEI for 1- Hydroxypyrene: Is it Protective?

Glenn Talaska
Department of Environmental Health
University of Cincinnati

Background: PAH BEI

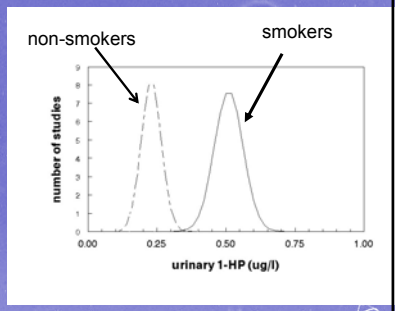
- Adopted 2005
- 1-hydroxypyrene (1HP) marker of current choice
- NQ….with a benchmark (1ug/l)
- Data not strong enough to support TLV equivalent or to be based on health effects
- Adjustment provided for mixtures with different benzo(a)pyrene: pyrene ratios

Why 1HP?

- Pyrene is abundant in most PAH mixtures
- Physical behavior approximates 4+ ring PAHs
- ~85% metabolized to 1HP
- Compared to BAP….2.5 times more common, and many fewer metabolites
- Pyrene is non-carcinogenic…Is 3-OHBAP associated with risk or detoxification?

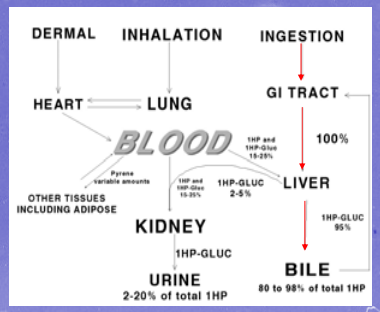
1HP Benchmark, 1 ug/l

- Based on distribution of non-exposed population
- Smokers and non-smokers have different curves;
- Less than 1% of population background will exceed 1.0ug/l



Impact of Diet on 1HP Levels

- Ingested PAH are metabolized by the liver first pass and eliminated in the bile
- NHANES study reported a 95%tile of 0.747 in all males not controlling for diet



Medications?

- Coal tar for dermal conditions is definitely a confounder….but easy to ask about

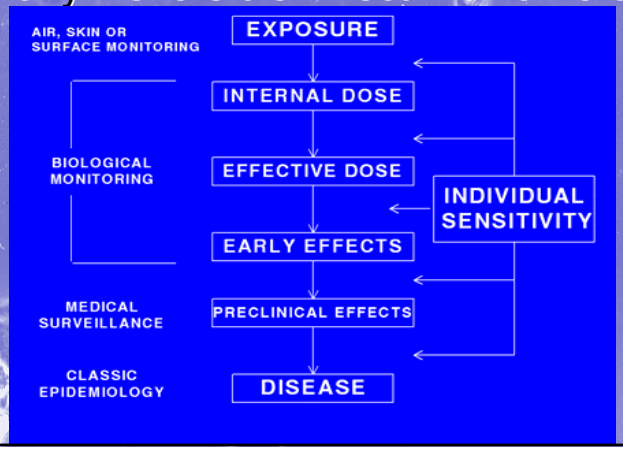
Will the BEI be protective? (Is a health-based BEI possible?)

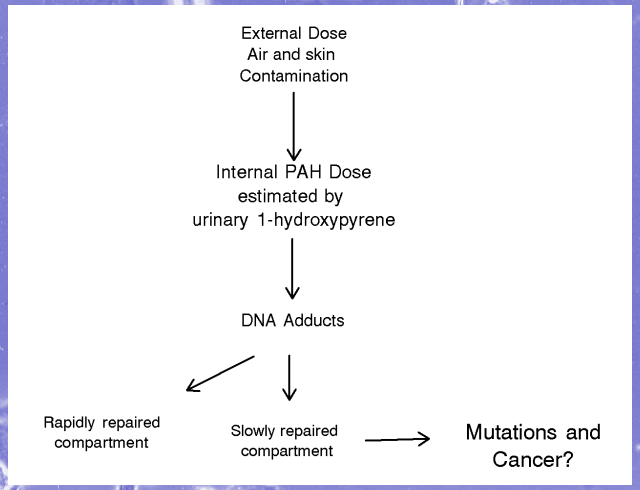
- Approaches
  - –Relate 1HP levels to disease cases
    - Epidemiology Studies
  - –Relate 1HP levels to effect biomarkers
    - Molecular Epidemiology Studies

1HP and Disease Incidence

- Are cancer incidence studies possible?
  - – What is the exposure window captured by 1HP?
  - – Half lives are 5.5, 23 and 384 hours
  - – Post shift 1HP measures the current day's exposure
  - – Pre-shift Monday 1HP estimates cumulative exposure
- Is there day to day exposure variability?

Can 1HP levels be related to Early/Reversible Effect Biomarkers?





Can 1HP levels be related to Early/Reversible effect Biomarkers?

- Assumptions
  - 1HP levels predict total and carcinogenic PAH exposures
  - PAH exposures cause DNA adducts or other damage (e.g., chromosomal damage)
  - DNA adducts levels are related to disease risk

1HP and DNA Adducts

- Godschalk/Van Schooten Studies
  - Applied coal tar for psoriasis
  - Saw 0.75 correlation with skin adducts and 1HP levels; r=0.74 for skin and monocytes; r=0.64 for skin and lymphocytes and r=0.44 for skin and granulocyte adducts (NS).
- Aluminum Workers r=0.66
- Many other studies negative…?

Target Organ Effects?

- Leukocytes in Blood
  - 8% monocytes + 25% lymphocytes+ 67% granulocytes
  - Granulocytes are in the blood for a few hours; short exposure window….
- Skin cells, monocyte/lymphocyte and exfoliated cell adducts are better correlated with exposure markers for PAH

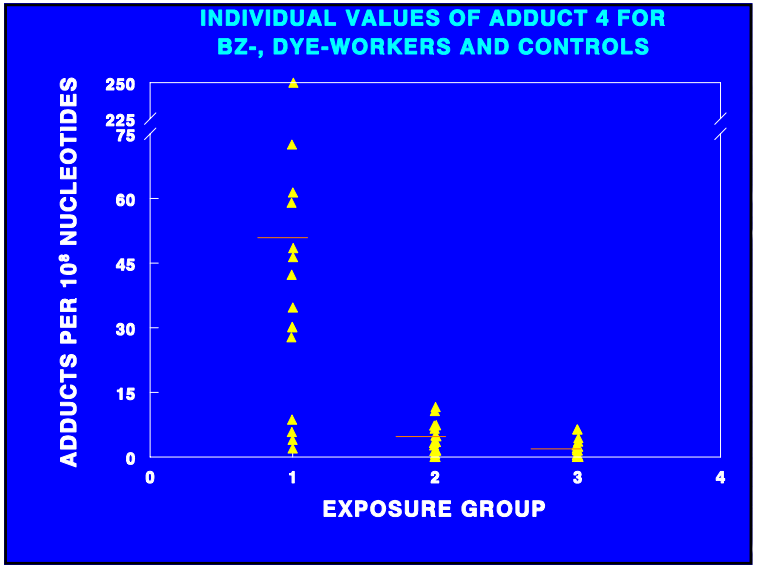
Target Organ DNA Adducts and Cancer

- Supported by animal studies
  - Beland
- Groopman studies in China
  - Synergy between aflatoxin adducts and hepatitis B
- Veglia showed that adduct levels could be used categorically to predict lung cancer risk
- Studies in our lab with benzidine, tobacco smoke are similar

BENZIDINE IN CHINA

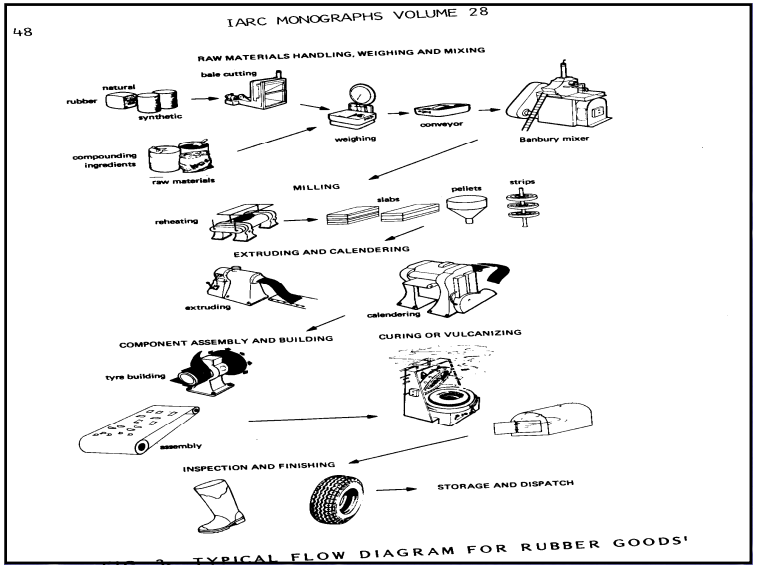
- **Production stopped in 1977**
- **Bi, et al, 1992***
  - **Overall a 25 fold excess risk**
    - **4.8 fold excess in "low" group**
    - **36.2 fold excess in "medium"**
    - **158 fold excess in "high" exposure**
- **Hayes, et al, 1993** saw that acetylation phenotype did not affect risk**

*Am. J. Ind. Med., 21,481-90. **Carcinogenesis, 14, 675-78.



Rubber workers Studies Processes in Rubbermaking

- Scaling
- Banbury Mixing
- Calendering
- Assembly and Building
- Curing or Vulcanizing
- Finishing



TYPICAL FLOW DIAGRAM FOR RUBBER GOODS[1]

Exposures in Dutch Rubberworks

- Documented decrease in total and specific dusts over the last 10 years
- Health effects (urinary bladder cancer) still elevated in latest reports for the industry

PAH Exposure in Rubberworks

- Exposure Sources
  - Extender Oils: 20+% of total rubber weight
    - Coal tar pitch, bitumen, aromatic oils
    - 4-6 ring PAH are 30% of total in aromatic oils
  - Carbon Blacks
    - Change from channel black to furnace blacks
    - Significant PAH found in extracts
  - Aromatic amines may also be present

Methods

- Subjects
  - A total of 81 rubber workers provided samples for urinary mutagenicity and 1HP
  - 56 nonsmokers provided urine samples for DNA adduct analysis
  - 48 nonsmokers provided blood samples for leukocyte DNA adduct analysis

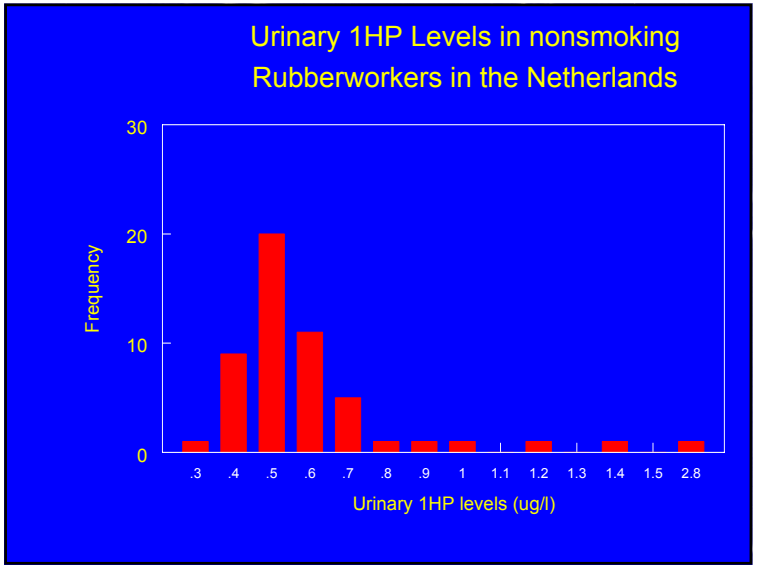
Results, DNA Adducts in Exfoliated Urothelial Cells and Blood Leucocytes

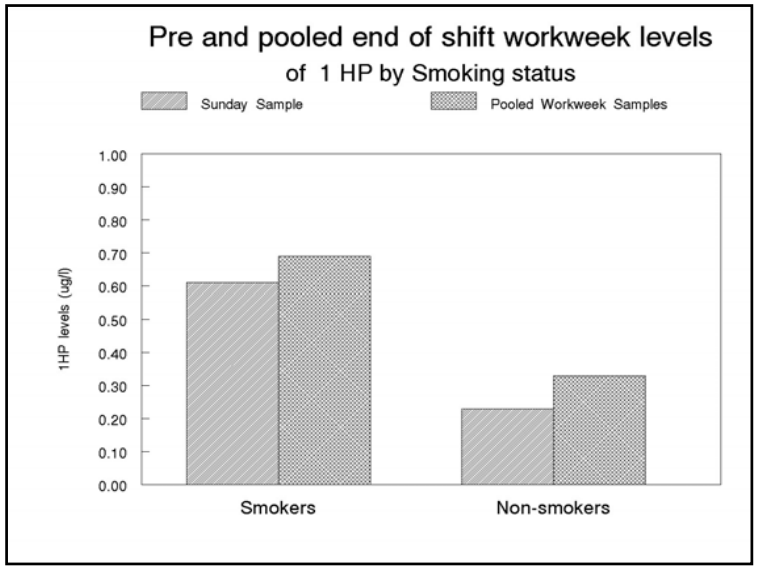
- Sufficient urothelial cell DNA was obtained in 52 of 56 subjects
- There was no association between urothelial cell and leucocyte DNA adduct levels
  - Neither in total or by individual adduct
- Leucocyte adducts were not associated with factory, department, 1HP or urinary mutagenicity.

Different exposure sources for 1HP and urinary mutagenesis

Marker	Exposure	β(se)	P
1HP	Inhalable dust	-0.05(0.08)	0.51
	Rubber fumes*	0.29(0.13)	0.02
	Dermal*	0.13(0.05)	0.02
Mutagenicity	Inhalable dust	0.22(0.13)	0.08
	Rubber fumes*	0.15(0.2)	0.43
	Dermal*	0.03(0.09)	0.7

*cyclohexane soluble materials





P values for type 3 tests of fixed effects of factory and department on biomarkers

Model	Fixed Effect				
		1HP	Mutat.	Uro adds	WBC
1	Factory	0.174	0.6874	0.6908	0.605
2	Dept.	0.019	0.0582	0.0001	0.9136
3	Factory	0.180	0.804	0.888	0.475
	Dept.	0.025	0.106	0.0016	0.728
4	Factory	0.106	0.800	0.089	0.8512
	Dept	0.010	0.336	0.0001	0.770
	F X D	0.004	0.930	0.0029	0.914

Net 1HP (ug/l) and Production Function

	N	GM	P value*
Mixing	10	0.0	0.490
Pre-treating	16	0.06	0.305
Molding	28	0.14	0.06
Curing	28	0.24	0.003
Finishing	11	0.08	0.555
Lab	2	0.0	
Shipping	4	0.06	.114
*Paired t test (weekday-Sunday) levels			

Association between 1HP, muU, UroAdds and WBC

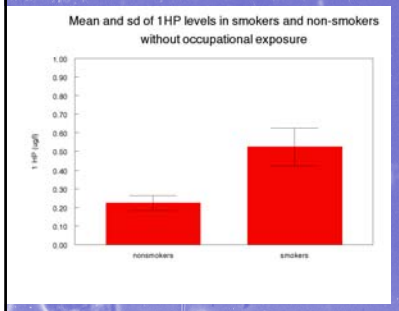
Model	β (SE)	P
1HP as predictor		
Urinary mutagenicity (muU)	0.18 (0.18)	0.315
Total Urothelial Adducts	1.4 (0.68)	0.035
Adduct 1	0.41 (0.48)	0.387
Adduct 3	0.92 (0.49)	0.058
WBC Adducts	-0.8 (0.65)	0.217
Predictor: Urinary mutagenicity		
Total Urothelial Adducts	0.75 (0.34)	0.03
Adduct 1	0.59(0.29)	0.04
Adduct 3	0.35(0.26)	0.18
WBC Adducts	-0.58 (0.46)	0.20

Conclusions from Rubber worker Studies

- Leucocyte DNA adduct levels not useful for PAH
- Urinary mutagenicity and 1HP seem to result from different exposures and these exposures produce different adducts
- PAH exposure via cured rubber contributes to 1HP and DNA adduct levels.
- Mixing is associated with MuU (aromatic amines?)
- Significant associations between 1 HP and urothelial DNA adduct levels at levels below benchmark.

Summary of urothelial adduct/metabolite studies

- Benzidine exposure: adduct levels proportionate to metabolites and risk (aromatic amines)
- Active smoking: adduct levels proportionate to BC risk, 1 HP levels seem to under-represent risk (aromatic amines?)



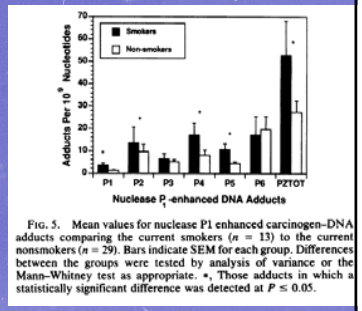


FIG. 5. Mean values for nuclease P1 enhanced carcinogen–DNA adducts comparing the current smokers (n = 13) to the current nonsmokers (n = 29). Bars indicate SEM for each group. Differences between the groups were tested by analysis of variance or the Mann–Whitney test as appropriate. *, Those adducts in which a statistically significant difference was detected at $P \leq 0.05$.

Summary of urothelial adduct/metabolite studies

- Benzidine exposure: adduct levels proportionate to metabolites and risk (aromatic amines)
- Active smoking: adduct levels proportionate to BC risk, 1 HP levels seem to under-represent risk (aromatic amines?)
- Passive smoking: adducts and 1HP levels not correlated….adducts 1.8X increased, risk ???

Questions….

- If adducts are increased in proportion to 1HP levels, can they be used as the effect level for increases in 1HP?
- Where do adduct levels above the population background become biologically significant with the object to protect worker health ?

Issues when using DNA adducts as risk estimates

- Between lab variability is large
- However, within lab variability is much better especially relative to controls….there was no control group in our rubber workers study which limits the conclusions that can be drawn.

Health Based BEI for PAH

- Will not likely be set on one effect biomarker, or on a single measurement of internal dose
- A web of evidence along the causal pathway is needed including DNA adducts, chromosome damage, DNA fragmentation and other tests in studies which include multiple measurements of external exposure and internal dose.

Future Studies

- Coke oven workers
  - 1HP and urothelial DNA adduct levels with dermal and air exposure estimates
- Patients being treated with coal tar.

References

- http://web2.airmail.net/uthman/blood_cells.html
- *Cancer Epidemiol. Biomarkers Prev.* 7, 767-773.
- *Cancer Epidemiol. Biomark Prev.* 17, 1452-1459.
- *Proc. Natl. Acad. Sci. U.S.A.* 93, 7789-7793.

Thank You....Merci!