AMERICAN PETROLEUM INSTITUTE

BENZENE

RESEARCH PROGRAM

PRESENTATION BY
COSMO DIPERNA

TO THE
HEALTH AND ENVIRONMENT
GENERAL COMMITTEES

MARCH 20, 1991

BENZENE -Why Important?

Component in major products.

Causes leukemia at high doses.

Federal and State policies lead to stringent controls.

1991 RESEARCH COSTS
($ THOUSANDS)

U of Colorado	**365**	**(115 CMA)**
CIIT	**250**	
Biological Risk Assessment	**100**	
Exposure analysis	**50**	
Meta-analysis	**60**	
Alternative potency estimate	**204**	**(110 WSPA)**
Total	**1,029**	

INDUSTRY RESEARCH COSTS FOR BENZENE
($ Thousands)

Year	API	WSPA/CMA Additions
1987	560	200 WSPA
1988	570	200 WSPA, 100 CMA
1989	580	50 WSPA
1990	885	175 WSPA, 160 CMA
1991	698*	115 WSPA, 110 CMA

* Does not include $150K pending reprogramming request.

(Legislative / Regulatory–response)

BENZENE ENVIRONMENTAL ISSUES

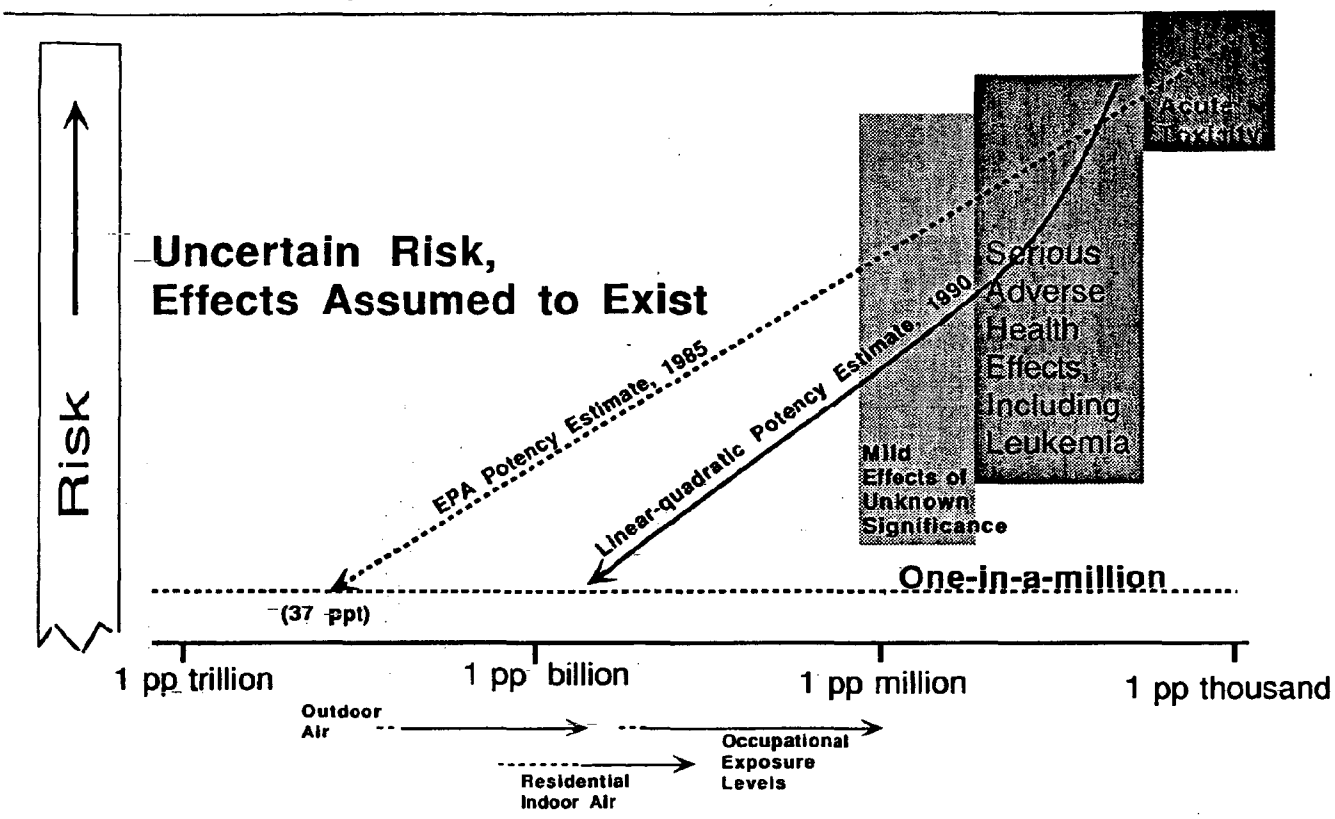
Air Toxics	10^{-6} risk fenceline controls (37 ppt)
Vehicle Emissions	One driving force for gasoline reformulation
Hazardous waste	TCLP of 0.5 ppm
Ground Water	5 ppb cleanup level*
Occupational exposure	Proposed ACGIH TLV of 0.1 ppm

*1 ppb in some-states

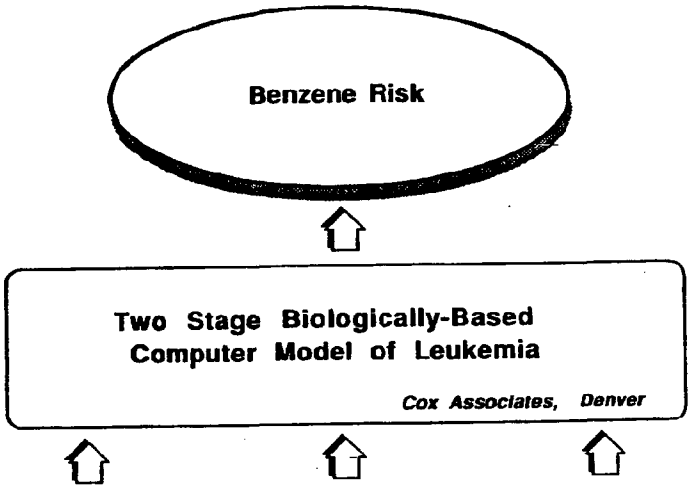
API–BENZENE PROGRAM

- Legislative /regulatory response
- Alternative potency estimate
- Fundamental toxicology research
- **Publish - Publish - Publish**

Potential Health Risk from Benzene at Ambient Exposure Levels



The API Benzene Program



Oak Ridge Nat'l Lab	*Chemical Industries Institute of Toxicology*	*University of Colorado*
In real environments, how much benzene is metabolized in the liver and bone marrow, in humans and laboratory animals?	In real environments, what are the concentrations of toxic metabolites in the bone marrow?	What bone marrow cell populations are at risk? How big are the populations? How rapidly do they divide? What are the frequencies of transformations? Are there other important effects on cells?
Physiologically-based Pharmacokinetics (PBPK) of Benzene	**Metabolite Identification and PBPKinetics in Whole Animals**	**Cell Kinetics and Effects of Toxic Metabolites in Human and Animal Marrow Cells**

Alternative potency estimate: New epidemiology data

HISTORY OF COHORT UPDATES

DOCUMENT	LATEST YEAR CONSIDERED	NUMBER OF WORKERS
1983 CRUMP AND ALLEN	1975	1866
1985 EPA POTENCY ASSESSMENT	1978	1866
1988 CLEMENT POTENCY ESTIMATE	1981	1866
1991 UPDATE OF THE COHORT[1]	1988	1291[2]

1 Three additional leukemias found in addition to the nine earlier cases
2 API will be asking EPA for help in completing the update

Alternative potency estimate

API POSITION ON 1985 EPA BENZENE POTENCY ASSESSMENT

- 1985 EPA Value - 26×10^{-6} at 1 ppb
  - 1×10^{-6} at 37 ppt

  - Updated cohort and exposure information not considered

  - Best available model should be applied to best available data

Alternative potency estimate: New exposure data

IDENTIFY NEW DATA AND REANALYZE EXISTING DATA (ChemRisk)

o Newly found data:
- production information
- interviews with Pliofilm workers
  - details of work practices
  - shift lengths
  - history of engineering controls

o Preliminary conclusions
- exposures were higher than previously thought
- workers at different plants had different exposures
- before the mid-1950's exposures were controlled by biological monitoring

o Current activities
- revise estimates of exposures which reflect
  - new information on engineering changes
  - dermal and peak inhalation exposures
- publish in the next few months

Alternative potency estimate: New exposure data

EXPOSURE ESTIMATES FOR THE PLIOFILM COHORT

1981	Original Rinsky study
1984	Crump and Allen develop individual worker exposure estimates
1985	EPA adopts Crump and Allen exposure estimates
1987	Rinsky develops alternative individual worker exposure estimates that are lower than Crump and Allen
1988	Kipen publishes API sponsored analysis of worker hematological data which supports Crump and Allen or higher estimates
1990-1	API sponsors new analysis of IH/workplace records

Alternative potency estimate: Model selection

SELECTION OF APPROPRIATE MODEL FOR BENZENE (ChemRisk)

- **Integrate and publish key findings of the last 5 years**
- **Reanalyze benzene potency using**
  - **the "best" linear and linear quadratic models**
  - **new epidemiology data**
  - **new exposure data**
  - **other cohorts as reality checks**
- **Perform sensitivity test for**
  - **disease endpoints**
  - **latency**
- **Examine other non-linear models**
- **Publish**

Alternative potency estimate: Choice of epidemiology studies

META-ANALYSIS
(Environ)

- **EPA used three studies: Pliofilm, Ott, and, Wong**
- **Georgetown conference recommended using Pliofilm alone and performing reality checks using Ott and Wong**
- **Meta-analysis project to determine the best way (if any) of combining epidemiology studies**

ISSUES WHICH CANNOT BE RESOLVED WITH CURRENT TOXICOLOGICAL DATA

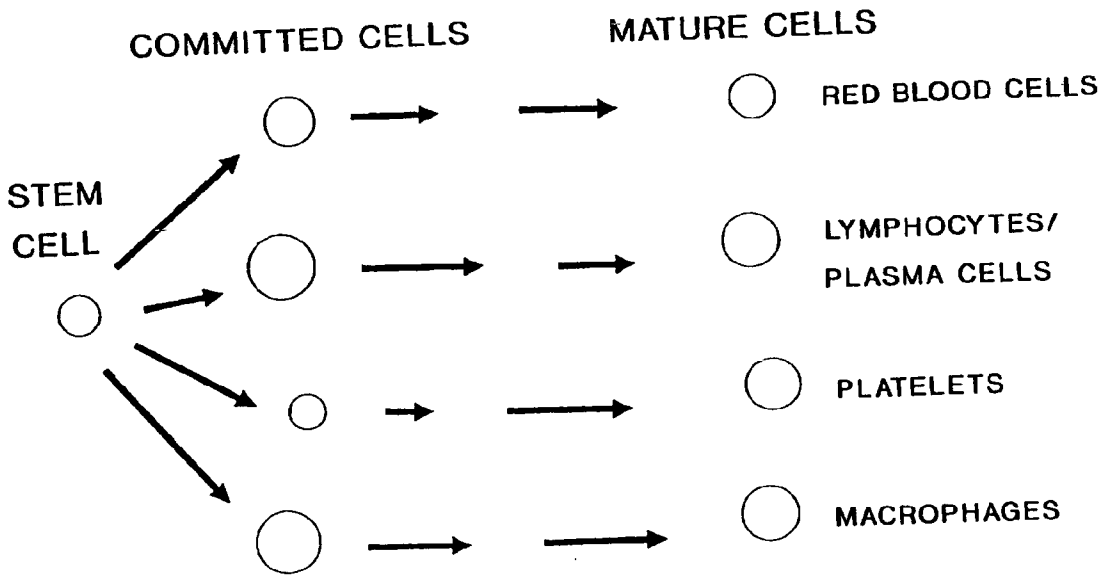
Do chronic exposures to small amounts of benzene present in the environment pose an unreasonable risk to humans?

Is there a concentration that does not present an unreasonable risk to humans?

PLANNED PUBLICATIONS:

1. NEW PLIOFILM EXPOSURE ESTIMATES
2. NEW PUBLICATION ON THE HEMATOLOGICAL RECORDS OF THE COHORT
3. ANALYTICAL METHODS USED TO MEASURE BENZENE IN OCCUPATIONAL SETTING BEFORE 1960
4. TEST OF FIT FOR RELATIVE AND ABSOLUTE MODELS
5. META-ANALYSIS OF BENZENE EPIDEMIOLOGY STUDIES
6. REVISED LINEAR AND LINEAR QUADRATIC POTENCY ASSESSMENTS

BONE MARROW CELLS



Fundamental toxicology research

BENZENE HAZARD STUDIES

(R. Irons & D. Ross, U. of Col.)

Goal: **Determine if benzene exerts toxic effects against the stem cell or at some later stage in blood formation. The latter would provide evidence that benzene is a threshold carcinogen.**

Research Questions:

- How are toxic effects manifested in bone marrow cells?
- How does benzene metabolism in bone marrow differ in animals and humans?
- Are high doses required to induce the cell changes that lead to leukemia?

Fundamental toxicology research

MODELING BENZENE MECHANISMS OF ACTION

Goal: **Construct general computer model accounting for the mechanism of benzene toxic effect in humans and animals.**

Research questions:

- What is the shape of the dose response relationship for benzene at ppb level?
- Is there a benzene concentration that does not present an unreasonable risk to humans (threshold question)?

Fundamental toxicology research

HAZARD STUDIES (CIIT)

Goal: **Determine the concentration of toxic metabolites in bone marrow and other organs**

Research Questions:

- What is the relationship between exposure (in ppm) and internal doses of metabolites in various animal target organs?
- How does benzene metabolism compare at high versus low doses?

REGULATORY LESSONS FROM API BENZENE ACTIVITIES

- Can not rush the process but need to:
  - Have ongoing research to keep current with the science
  - Peer review and publish new findings
  - Involve regulatory agencies at the Federal and State levels
  - Have high quality communication at all levels

CONCLUSION

- **If today is the decision day for ACGIH, then the Environ Risk Analysis, with the Crump/Allen exposure estimates, should be used.**
- **The resultant risk level at 1 ppm is the same as Rinsky's risk level at 0.1 ppm.**
- **Ongoing work to improve the Pliofilm exposure estimates should be published within the year.**
- **A new risk assessment will be performed using the updated Pliofilm Cohort and will also be published within the year.**

WHY IS THE PLIOFILM COHORT THE MOST APPROPRIATE FOR QRA?

- **Leukemia is the disease end-point in question for benzene.**
- **There is no question about the number of leukemias in the Pliofilm Cohort.**
- **Individual exposure estimates can be made for the members of the Pliofilm Cohort.**
- **There was an absence of significant exposures to other chemicals.**

WHAT IS THE PLIOFILM COHORT?

- **Pliofilm was a strong, thin flexible covering similar to Saran Wrap.**
- **It was manufactured by Goodyear from 1936 to 1976.**
- **The manufacturing process and the cohort was first described by Rinsky & Infante in 1981.**
- **Three plants at two locations:**
  - **Akron, Ohio**
  - **St. Marys, Ohio**
- **Cohort size (Crump/Allen, 1984): 1866 non-salaried white males.**

PRESENTATION OUTLINE

- **The Pliofilm worker cohort provides the best basis for developing a quantitative risk assessment (QRA) on benzene.**
- **The Pliofilm exposure estimates are critical to the outcome of the QRA.**
- **Crump/Allen (1984) exposure estimates are demonstratively more accurate than those used by Rinsky (1987).**
- **More recent research shows even higher exposure levels than Crump/Allen (1984) based on work patterns, production levels, engineering changes, early monitoring biases and dermal uptake data.**
- **Using the Rinsky (1987) risk model and the Crump/Allen (1984) exposure estimates, Environ researchers found that the level of risk at 1 ppm is equivalent to Rinsky's risk level at 0.1 ppm.**

PRESENTATION BY:

Cosmo Di Perna (Mobil)
Chairman Of API'S Benzene Issues Group

Joseph Rodricks, Ph. D. - Environ Corporation

Dennis Paustenbach, Ph. D., CIH, DABT
Chemrisk--A Division Of Mclaren/Hart

PRESENTATION OF

AMERICAN PETROLEUM INSTITUTE

AND

WESTERN STATES PETROLEUM ASSOCIATION

TO THE

AMERICAN CONFERENCE OF GOVERNMENT INDUSTRIAL HYGIENISTS

MARCH 26, 1991

NEW ANALYSIS

YET UNPUBLISHED

PAUSTENBACH et al. 1991

DERMAL UPTAKE

$$\text{Uptake} = N \times SA \times ET \times RA \div BW$$

N = Number of contacts per day

SA = Surface area exposed

ET = Duration of exposure

RA = Rate of adsorption

BW = Body weight

EVIDENCE THAT BENZENE EXPOSURES TO BENZENE WERE LIKELY HIGHER THAN ESTIMATED BY CRUMP/ALLEN

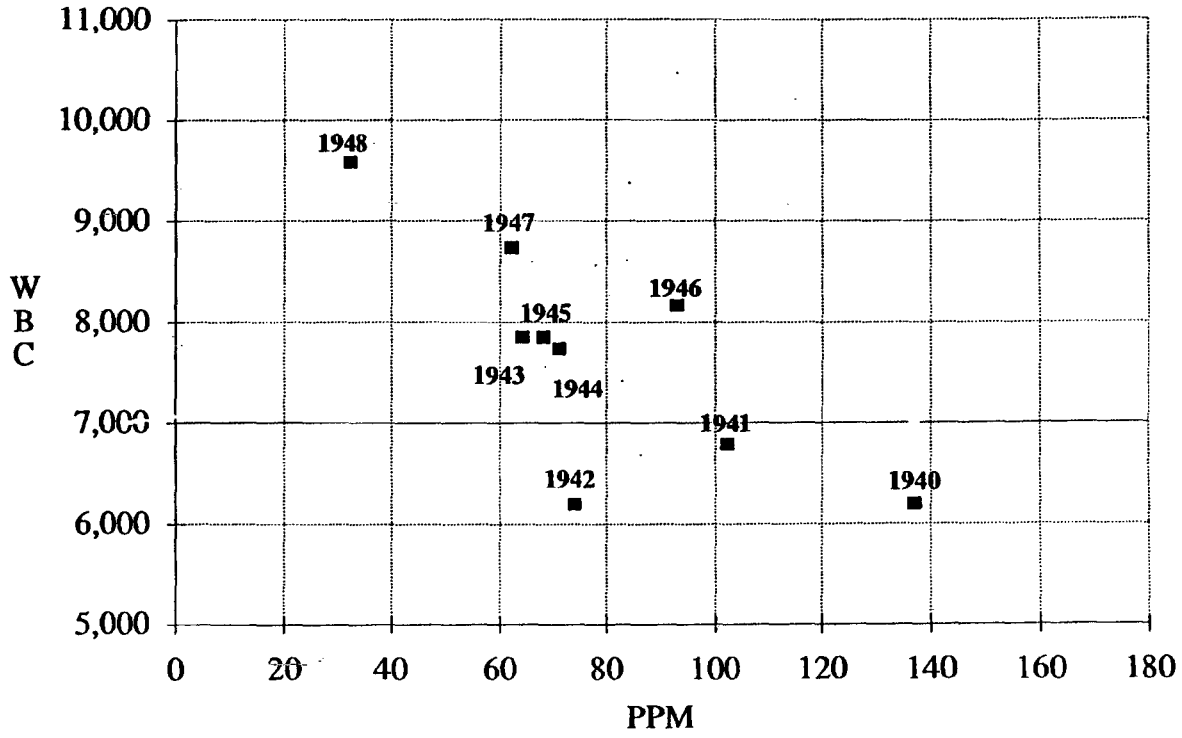
- Air monitoring data for benzene concentrations, used by both Rinsky and Crump/Allen, underestimated exposures.
  - detector tubes read 40% too low (Hay, 1969)
  - combustible gas indicators read about 100% too low (Pagnatto, 1961, Cook, 1947)
- Extended work weeks were common after 1942.
- IH standards were relaxed during 1941-45 (Department of Labor 1942, Rothman 1942).
- Crump/Allen attempts to characterize peak exposures were limited by available data.
- Medical monitoring (blood counts) was used in place of air sampling to manage worker exposures.

OTHER EVIDENCE THAT CRUMP/ALLEN IS MORE ACCURATE THAN RINSKY

- Rinsky estimates are inconsistent with reported cases of benzene toxicity among pliofilm workers in the early 1940s (Conn 1942, Wilson 1942) and reports of workers in the 1940s and 1950s being removed from production jobs because of depressed blood counts.

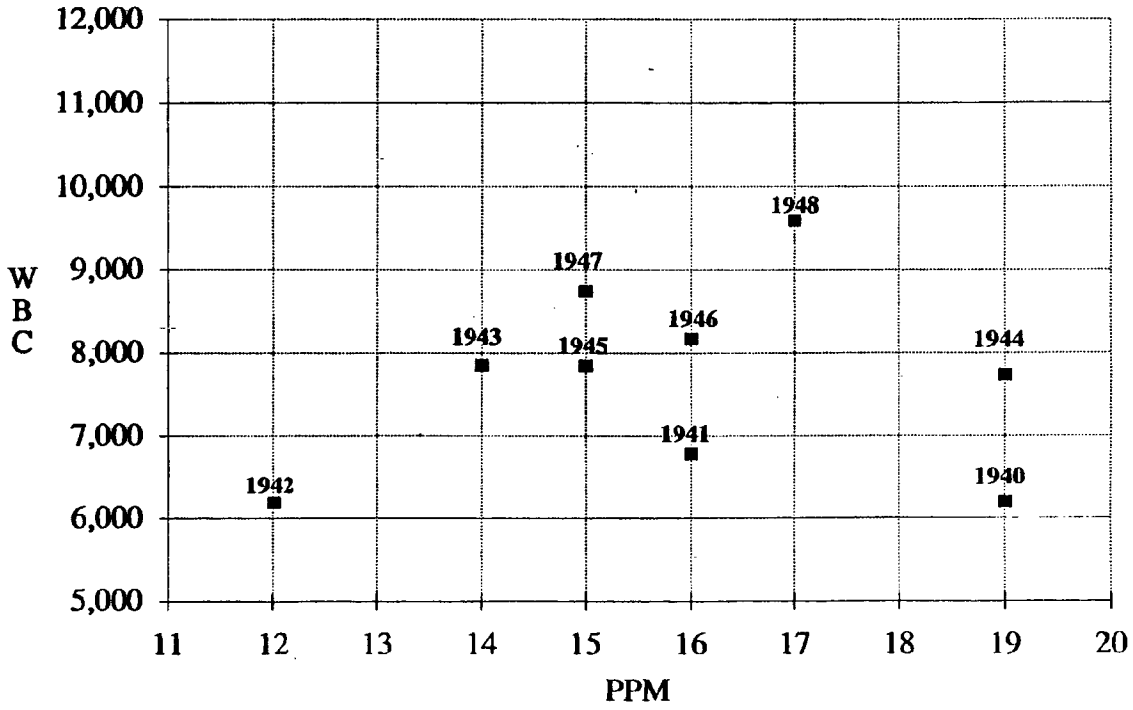
- Industrial hygienists' reports of difficulties in meeting benzene standards before 1950s (Hamilton 1922, Greenburg, 1930, Sappington 1940, Stockinger 1955).

CRUMP/ALLEN (1984) BENZENE EXPOSURE ESTIMATES VS. WHITE BLOOD COUNTS



R= -0.76 p= 0.016

RINSKY (1987) BENZENE EXPOSURE ESTIMATES VS. WHITE BLOOD COUNTS



R= -0.05 p=0.89

FINDINGS OF KIPEN et al. (1989)

- Strong correlation between annual averages of blood counts at St. Marys and Crump/Allen exposure estimates.

- No correlation between blood counts and Rinsky exposure estimates.

PLIOFILM WORKER BLOOD DATA*

- Biological monitoring data - red blood counts and white blood counts - collected at the St. Marys plant.

- Approximately 1,700 samples taken from 459 workers between 1940 and mid 1970s.

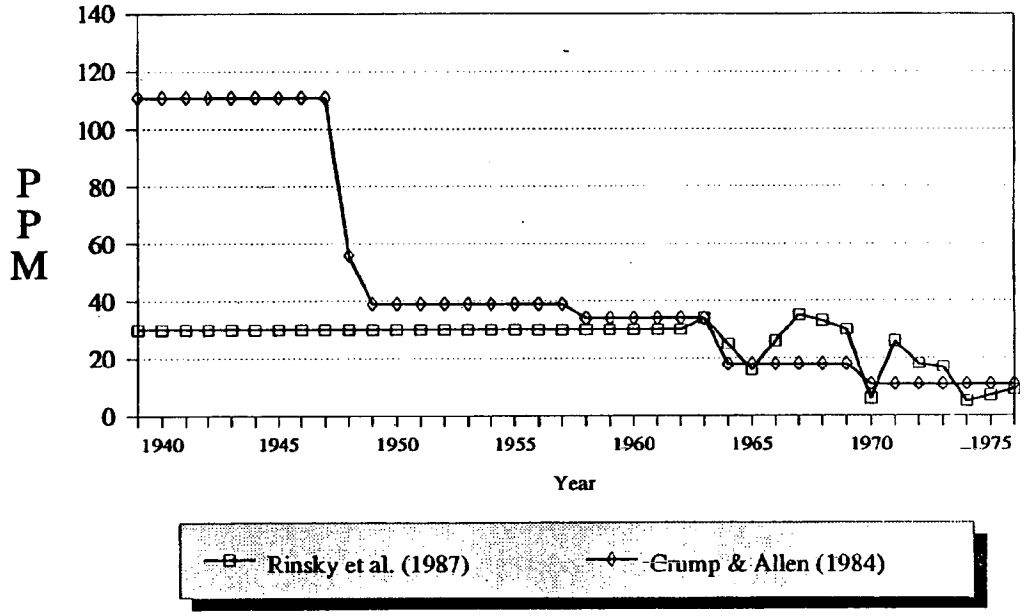
- Data not considered by either Crump/Allen or Rinsky.

*Kipen et. al. (1989)

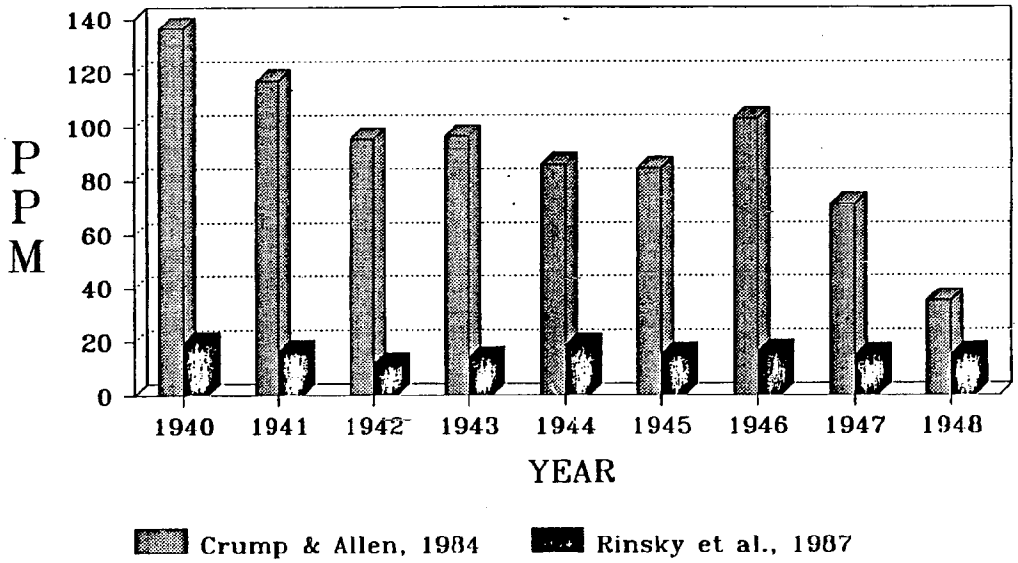
WHICH SET OF ESTIMATES IS MORE ACCURATE?

Peripheral blood count measurements of Pliofilm workers support Crump/Allen assumption of increasing worker exposures backward in time.

AVERAGE BENZENE EXPOSURE FOR "QUENCHER" JOB IN THE PLIOFILM COHORT



AVERAGE ANNUAL BENZENE EXPOSURES FOR THE PLIOFILM COHORT (St. Marys)



Source: Kipen et al. (1989)

HOW DO THE RINSKY AND CRUMP/ALLEN BENZENE EXPOSURE ESTIMATES DIFFER

- In the absence of monitoring data during the 1940s and early 1950s:
  - Crump/Allen assumed increasing exposures backwards in time to 1940.
  - Rinsky assumed a constant level of exposure over the period.
- After the early 1950s, the two analyses show only minor differences in exposure estimates despite differing assumptions in selection and use of available monitoring data.

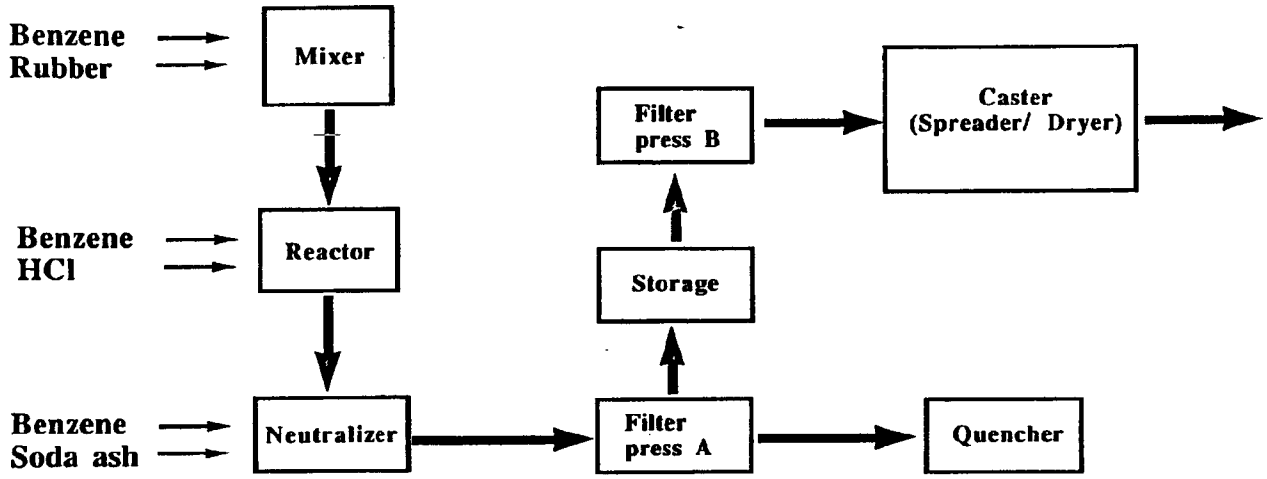
PLIOFILM EXPOSURE ESTIMATES:

- Rinsky et al. (1987)
- Crump and Allen (1984)
- Paustenbach et al. (1991)

CHANGES IN BENZENE TLV OVER TIME

1940	100 ppm (State of Mass.)
1946	100 ppm
1947	50 ppm
1948	35 ppm
1957	25 ppm
1963	25 ppm - skin
1977	10 ppm

SIMPLIFIED SCHEMATIC DIAGRAM OF PLIOFILM PROCESS



ESTIMATES OF OCCUPATIONAL EXPOSURE FOR THE PLIOFILM COHORT: IMPLICATIONS FOR SETTING A TLV FOR BENZENE

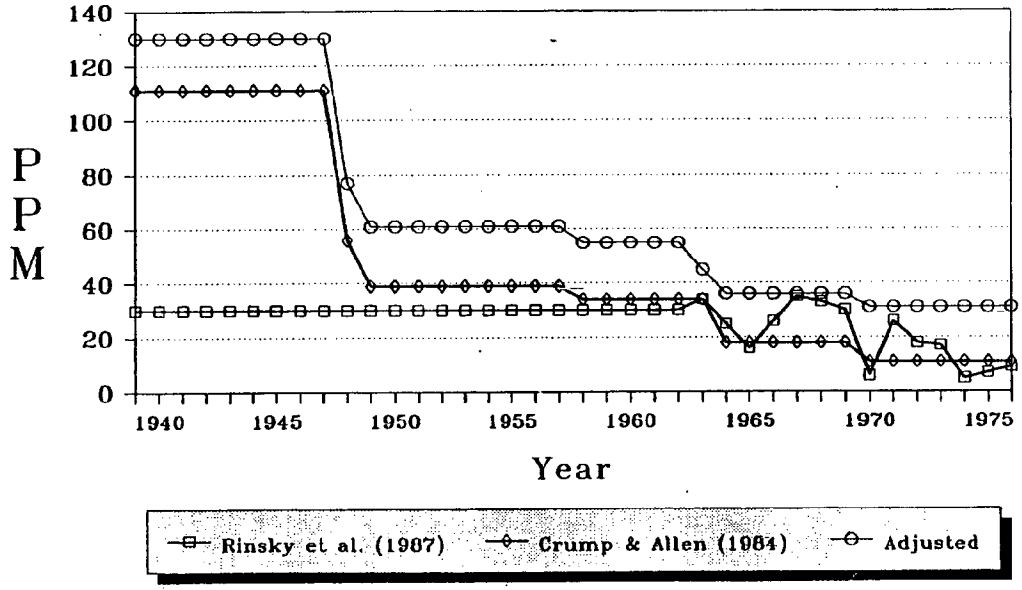
March 26, 1991

Dennis J. Paustenbach, Ph.D., CIH, DABT*

ChemRisk--A Division of McLaren/Hart
Alameda, California

* on behalf of the American Petroleum Institute

AVERAGE BENZENE EXPOSURE FOR "QUENCHER" JOB IN THE PLIOFILM COHORT



PAUSTENBACH et al. 1991

Quantitatively accounts for:

- Dermal uptake
- Peak exposures
- Monitoring biases
- Engineering changes
- Production levels

CONCLUSIONS

- Rinsky (1987) exposure estimates are highly unlikely: exposures in the 1930s and 1940s were higher than in the mid 1950s.
- Crump/Allen (1984) exposure estimates represent a more accurate characterization and are consistent with worker blood data.
- New exposure estimates will incorporate information not available to either Rinsky or Crump/Allen.
- Revised estimates will be sufficiently different from either prior analysis and should be considered when setting a new TLV.

PRESENTATION TO DR. WILLIAM FARLAND
MARCH 19, 1991

PURPOSE OF API - WSPA VISIT TO EPA
July 13, 1990

- o REVIEW RATIONALE FOR REOPENING POTENCY ASSESSMENT
- o SUMMARIZE API PAST POTENCY ASSESSMENT EFFORTS
- o DISCUSS API'S CURRENT EFFORTS TO IMPROVE POTENCY ESTIMATE
- o REVIEW API'S LONG TERM RESEARCH EFFORTS

API -WSPA- EFFORTS TO IMPROVE BENZENE POTENCY ASSESSMENT
July 13, 1990

- o CONTRACT CHEMRISK (DR. DENNIS PAUSTENBACH) TO INTEGRATE AND PUBLISH KEY FINDINGS OF THE LAST FIVE YEAR'S RESEARCH EFFORTS
- o USE PLIOFILM COHORT AS THE BASIS FOR POTENCY ASSESSMENT AND OTHER STUDIES AS REALITY CHECKS
- o EXAMINE THE LINEAR-QUADRATIC AND MKV MODELS
- o SEEK CONSENSUS ON:
  - LATENCY PERIOD - SELECTION OF ENDPOINTS
  - DOSE METRIC - RELATIVE VS. ABSOLUTE
- o OBTAIN PEER REVIEW OF RESULTS

PURPOSE OF TODAY'S VISIT

- STATUS OF API - WSPA PROGRAM ON BENZENE POTENCY ASSESSMENT
- EPA INTEREST IN REOPENING BENZENE POTENCY
- STATUS OF API LONG TERM RESEARCH PROGRAM

BENZENE POTENCY ASSESSMENT ISSUES

- o DATA ISSUES
  - CHOICE OF EPIDEMIOLOGY STUDIES
  - SIGNIFICANCE OF DISEASE ENDPOINTS
- o PLIOFILM COHORT ISSUES
  - UPDATE OF COHORT
  - EXPOSURE ESTIMATES
  - INTERPRETATION OF BLOOD COUNTS
- o MODELING ISSUES
  - LATENCY
  - RELATIVE VERSUS ABSOLUTE RISK
  - INDIVIDUAL TRANSITION RATE
- o REVISED POTENCY ESTIMATES
  - LINEAR MODEL
  - NON-LINEAR MODELS

DATA ISSUES: CHOICE OF EPIDEMIOLOGY STUDIES

- **EPA USED THREE STUDIES**
- **GEORGETOWN RECOMMENDED USING PLIOFILM AND PERFORMING REALITY CHECKS USING OTT AND WONG**
- **META-ANALYSIS PROJECT TO DETERMINE POSSIBLE ADVANTAGES OF COMBINING EPIDEMIOLOGY STUDIES**

DATA ISSUES: SIGNIFICANCE OF DISEASE ENDPOINTS

- **DETERMINE THE EFFECT OF ENDPOINT SELECTION OF POTENCY ESTIMATE**

- **ESTIMATE BENZENE POTENCY USING:**
  - **AML ONLY**
  - **TOTAL LEUKEMIAS**
  - **TOTAL LEUKEMIAS PLUS MULTIPLE MYELOMAS**
  - **OTHERS**

HISTORY OF COHORT UPDATES

DOCUMENT	LATEST YEAR CONSIDERED	NUMBER OF WORKERS
1983 CRUMP AND ALLEN	1975	1,866
1985 EPA POTENCY ASSESSMENT	1978	1,866
1988 CLEMENT POTENCY ESTIMATE	1981	1,866
1991 UPDATE OF THE COHORT	1988	1,291

RESULTS OF THE UPDATE

1982-83	**NO ADDITIONAL LEUKEMIA**
1984	**1 MYELOCYTIC LEUKEMIA**
1985	**1 MYELOCYTIC LEUKEMIA** **1 LYMPHATIC LEUKEMIA**
1986-88	**NO ADDITIONAL LEUKEMIA**

NO ADDITIONAL CASES OF MULTIPLE MYELOMA

API - WSPA EFFORTS ON PLIOFILM EXPOSURE ESTIMATES

- NEWLY FOUND DATA:
  - PRODUCTION INFORMATION
  - INTERVIEWS WITH PLIOFILM WORKERS

    SIGNIFICANT ENGINEERING CONTROLS WERE INTRODUCED IN THE LATE 1940S IN BOTH PLANTS

    RELIANCE ON BIOLOGICAL MONITORING NOT AIR SAMPLING FOR BENZENE CONTROL

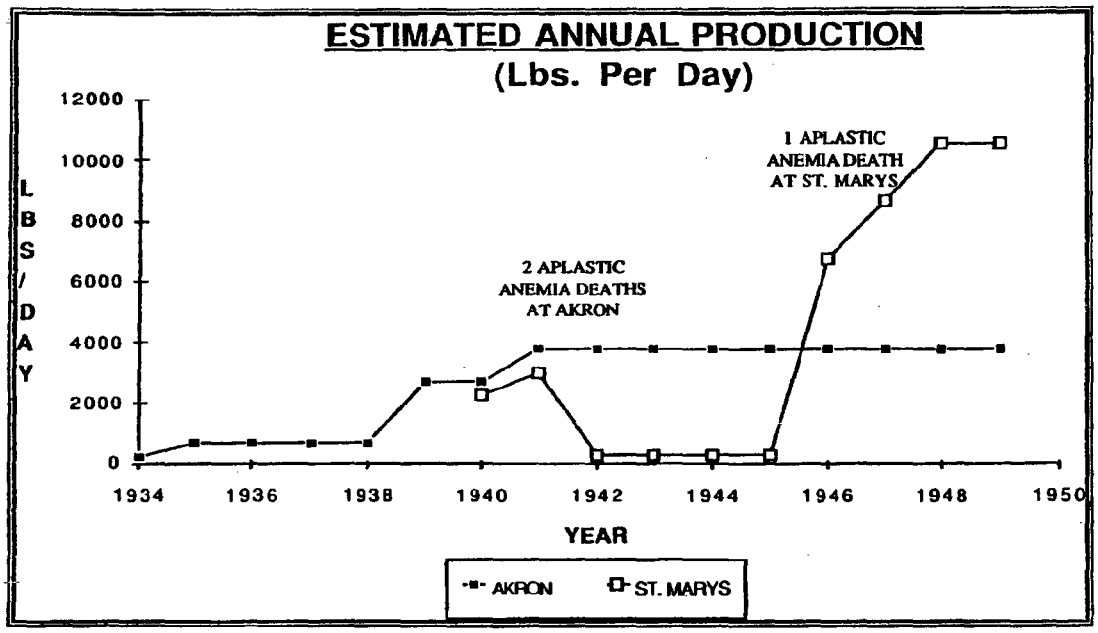
    SIX AND SEVEN DAY SHIFTS COMMON

    PEAK AND DERMAL EXPOSURES WERE SIGNIFICANT

INTERPRETATION OF NEW DATA (PRELIMINARY CONCLUSIONS)

- **EXPOSURES ARE LIKELY TO BE HIGHER THAN CRUMP-ALLEN FOR MOST WORKERS FOR MOST YEARS**
  - **BIASES IN ANALYTICAL METHODOLOGY**
  - **PEAK EXPOSURES NOT CONSIDERED FOR MANY JOB CLASSIFICATIONS**
  - **DERMAL NOT CONSIDERED**
- **ST. MARYS DIFFERED FROM AKRON IN THE 1940'S**
  - **ST. MARYS LARGELY SHUT DOWN DURING 1942-1945 DUE TO SHORTAGE IN RUBBER SUPPLIES**
  - **ST. MARYS INSTALLED BENZENE CONTROLS IN 1946 WHICH WERE NOT IN PLACE IN AKRON PLANT**
  - **MORE FREQUENT BLOOD MONITORING**
- **BEFORE THE MID 1950'S GOODYEAR RELIED ENTIRELY ON BIOLOGICAL MONITORING FOR BENZENE EXPOSURE CONTROL**

PLIOFILM COHORT ISSUES: EXPOSURE ESTIMATES



PLIOFILM COHORT ISSUES: EXPOSURE ESTIMATES

CURRENT ACTIVITIES

- REVISE ESTIMATES OF AREA CONCENTRATIONS IN THE 1940'S TO REFLECT NEW INFORMATION ON ENGINEERING CHANGES AT ST MARYS
- PERFORM TIME AND MOTION STUDIES TO CHARACTERIZE DERMAL AND PEAK INHALATION EXPOSURES
- DEVELOP "TOTAL" TWA ESTIMATES OF SHIFT EXPOSURES
- PUBLISH OVER THE NEXT FEW MONTHS

PLIOFILM COHORT ISSUES: INTERPRETATION OF BLOOD COUNTS

- NEW ANALYSIS OF WORKER DATA CONFIRMS PRELIMINARY CONCLUSION OF KIPEN ET.AL 1989, THAT TEMPORAL BLOOD COUNT TRENDS WERE NOT AN ARTIFACT OF THE DATA SET

- ADDITIONAL DATA SUGGEST THAT WORKERS IN HIGHLY EXPOSED JOB CLASSIFICATIONS CAN BE DIFFERENTIATED FROM WORKERS WITH MODERATE AND LOW EXPOSURES

- ARTICLE WILL BE SUBMITTED TO PEER REVIEW JOURNAL WITHIN NEXT TWO MONTHS

MODELING ISSUES: LATENCY

LATENCY:

- o BASE LATENCY ON RADIATION OR PLIOFILM COHORT ITSELF
- o GEORGETOWN RECOMMENDED THE PLIOFILM COHORT
- o PERFORM SENSITIVITY ANALYSIS

CHOICE OF RISK MODEL

- 1985 EPA POTENCY ESTIMATE USED BOTH
- FOLLOW-UP OF PLIOFILM COHORT OFFERS AN OPPORTUNITY TO TEST APPROPRIATENESS OF MODELS

MODELING ISSUES: RELATIVE VERSUS ABSOLUTE RISK

PRELIMINARY ANALYSIS OF COHORT DATA THROUGH 1981 SUGGESTS THAT RELATIVE RISK MODEL OF PLIOFILM COHORT DOES NOT FIT OBSERVED DATA

TIME PERIOD	NUMBER OF CASES PREDICTED BY RELATIVE RISK MODEL	NUMBER OF CASES OBSERVED
1940 - 1953	3.0	1
1954 - 1967	5.7	7
1968 - 1981	6.9	1

API - WSPA PLAN TO UPDATE THIS WITH NEW COHORT DATA AND PUBLISH THIS YEAR

INDIVIDUAL TRANSITION RATE

(TREAT WORKERS AS INDIVIDUALS RATHER THAN COMBINING INTO SIX DOSE GROUPS)

- **STATISTICALLY MORE EFFICIENT**
- **RECOMMENDED BY GEORGETOWN**

REVISED POTENCY ESTIMATE : LINEAR MODEL

- o BASE ON PLIOFILM COHORT ALONE: OTT AND WONG TO BE USED AS A CHECK
- o NEW EXPOSURE AND COHORT DATA
- o INDIVIDUAL TRANSITION RATE
- o DIFFERENT LATENCY ASSUMPTIONS
- o DIFFERENT ENDPOINT ASSUMPTIONS
- o ABSOLUTE RISK AND RELATIVE RISK
- o SENSITIVITY ANALYSIS ON
  - ENDPOINTS
  - LATENCY
  - RELATIVE AND ABSOLUTE RISK

REVISED POTENCY ESTIMATE: NON-LINEAR MODEL

- **BENZENE: A CANDIDATE FOR NON-LINEAR MODELING**
  - **BEST FIT OF THE DATA**
- **EXPLORE LINEAR QUADRATIC AS ONE NON-LINEAR MODEL**
  - **GEORGETOWN RECOMMENDATION**
  - **LEUKEMIA INDUCED BY RADIATION FOLLOWS A NON-LINEAR MODEL**

PLANNED PUBLICATIONS:

1. NEW PLIOFILM EXPOSURE ESTIMATES
2. NEW PUBLICATION ON THE HEMATOLOGICAL RECORDS OF THE COHORT
3. PAPER ON ANALYTICAL METHODS
4. TEST OF FIT FOR RELATIVE AND ABSOLUTE MODELS
5. META-ANALYSIS
6. REVISED LINEAR AND LINEAR QUADRATIC POTENCY ASSESSMENTS

API'S LONG TERM RESEARCH PROGRAM ON

BENZENE TOXICOLOGY

STATUS OF RESEARCH

IRONS

PUBLICATIONS ON EFFECTS OF BENZENE METABOLITES ON HEMOPOIETIC SYSTEM PLANNED FOR MID 1991

COX

COX "PUBLICATIONS"

DEVELOPMENT OF PC BASED PBPK MODELS FOR BENZENE

THE NEXT STAGE IN MODELING

CIIT

WORK PROGRESSING

EPA/API INTERACTIONS:

- o LINDA BIRNBAUM ATTENDANCE AT OCTOBER MEETING WITH CIIT
- o TONY COX TO MAKE A PRESENTATION TO EPA STAFF IN RTP (LINDA BIRNBAUM) IN LATE APRIL
- o NEED TO DO BETTER:
  - CONTACT FOR BENZENE INFORMATION
  - ROUTINE ATTENDANCE OF EPA STAFF AT IN-TOWN MEETINGS OF BENZENE TOXICOLOGY WORKGROUP

LEUKEMIAS AND MULTIPLE MYELOMAS IN THE RINSKY COHORT						
CASE	ID	AGE AT DEATH	YEAR OF DEATH	CAUSE	RINSKY ARTICLE	NEW ICD (on current sheet)
1	000228	36	1958[a]	Monocytic leukemia	204	204.2
2	000123	29	1950[a]	Chronic myelogenous leukemia	204	204.1
3	000043	60	1958[a]	Acute myelocytic leukemia	204	204.3
4	000244	65	1960[a]	Acute myelogenous leukemia	204	204.3
5	000282	62	1961[a]	DiGuglielmos acute myelocytic leukemia	204	204.3
6	000240	57	1961[a]	Acute granulocytic leukemia	204	204.3
7	001013	57	1957[a]	Acute monocytic leukemia	204	204.2
8	001106	28	1954[a]	Myelogenous leukemia	204	204.1
9	000248	67	1979[c]	Acute myeloblastic leukemia	204	205.0
10	000140	69	1980[c]	Multiple myeloma	203	203
11	000460	52	1963[a]	Multiple myeloma	203	203
12	001079	62	1968[b]	Plasma cell sarcoma	203	203
13	001181	68	1981[c]	Multiple myeloma	203	203
14*	001109	82	1974[b]	FEMALE		205.0

LEUKEMIAS AND MULTIPLE MYELOMAS IN THE RINSKY COHORT (continued)						
CASE	ID	AGE AT DEATH	YEAR OF DEATH	CAUSE	RINSKY ARTICLE	NEW ICD (on current sheet)
15*	001290	67	1984[c]	Chronic myloid		205.1
16*	000465	67	1985[c]	Acute myloid		205.0
17*	000602	67	1985[c]	Acute lymphoid		204.0
18*	000190	71	1986[c]	Not Spec		208.9
19*	001126	81	1987[c]	Not Spec		208.9

FOOTNOTES

[a]ICD6-7
[b]ICD8
[c]ICD9
*New (not in article)

AKRON # pre 1949

UPDATE OF LEUKEMIA RISK POTENTIALLY ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO BENZENE

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caylus01-1972a rd2.01.032191

BASIS OF ACGIH TLV-TWA RECOMMENDATION OF 0.1 PPM

- Rinsky et al. (1987) analysis that suggests that "the odds of benzene-induced leukemic death at 0.1 ppm approach very nearly the odds of leukemic death for a worker who is not exposed to benzene."

RINSKY et al. 1987 RISK ANALYSIS

- **PRINCIPAL RINSKY ET AL. ASSUMPTIONS:**

  (i) Plioform cohort data are the best available for quantitative analysis.

  (ii) Conditional logistic regression best describes relation between OR and exposure.

  (iii) Rinsky et al. exposure matrix represents benzene exposures of Pliofilm cohort.

  (iv) Appropriate matching criteria (cases vs. controls) are date of birth and date of entering Pliofilm work.

- **ENVIRON analysis (Brett et al. 1989) reexamined these four assumptions.**

PREFERRED DATA SET FOR BENZENE RISK-ASSESSMENT

Rinsky et al. cohort of Pliofilm workers.

- Benzene as predominant exposure well established.
- Individual exposure estimates can be established for this cohort based on industrial hygiene data.

PREFERRED RISK MODEL FOR BENZENE RISK ASSESSMENT

Matched Case-Control Conditional Logistic Regression (Rinsky et al. 1987)

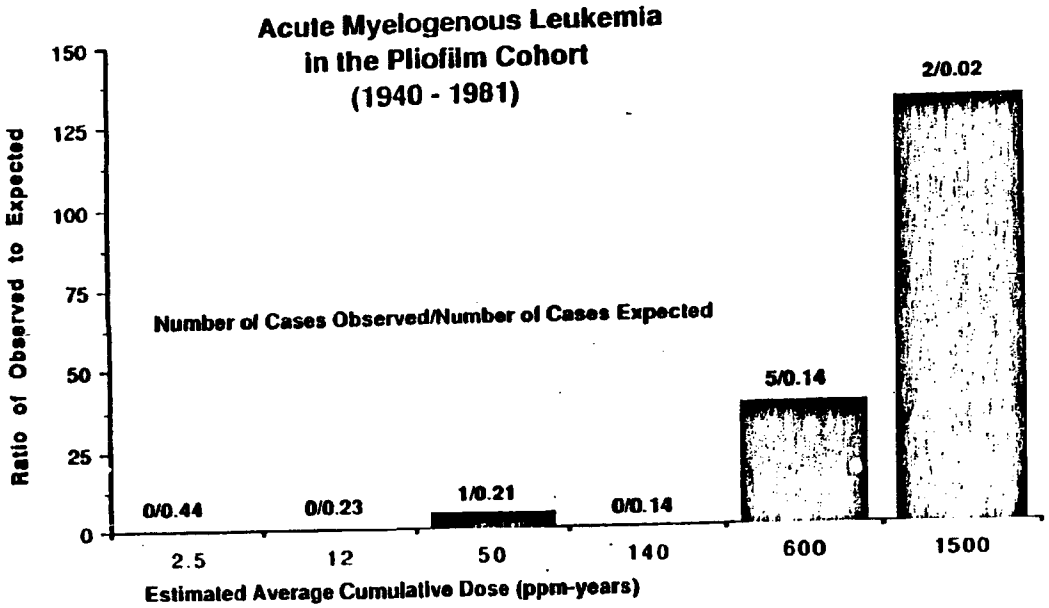
- Makes maximal use of data available on individual exposure levels.
- Avoids loss of information and resultant imprecision in analyses that dichotomize (e.g., linear and one-hit models) or categorize (Crump and Allen absolute and relative risk models) cumulative benzene exposure.

COMPARISON OF RINSKY ET AL. AND CRUMP/ALLEN EXPOSURE ESTIMATES

- The exposure estimates of Crump/Allen are generally higher than those of Rinsky for the majority of job titles and time periods covered.

- Crump/Allen exposure estimates appear more plausible because they are consistent with changes in the TLVs and with industrial hygiene practice over that time period.

DATES OF FIRST BENZENE EXPOSURE FOR 9 LEUKEMIA CASES (Rinsky et al., 1987)		
Case	**Year of First Exposure**	**Year of Death**
1	1941	1958
2	1948	1950
3	1944	1958
4	1944	1960
5	1939	1961
6	1941	1961
7	1942	1957
8	1951	1954
9	1942	1979


Acute Myelogenous Leukemia
in the Pliofilm Cohort
(1940 - 1981)
Ratio of Observed to Expected
150
125
100
75
50
25
0
Number of Cases Observed/Number of Cases Expected
0/0.44
0/0.23
1/0.21
0/0.14
5/0.14
2/0.02
2.5
12
50
140
600
1500
Estimated Average Cumulative Dose (ppm-years)

ALTERNATIVE CASE-CONTROL MATCHING CRITERIA FOR CONDITIONAL LOGISTIC REGRESSION ANALYSES

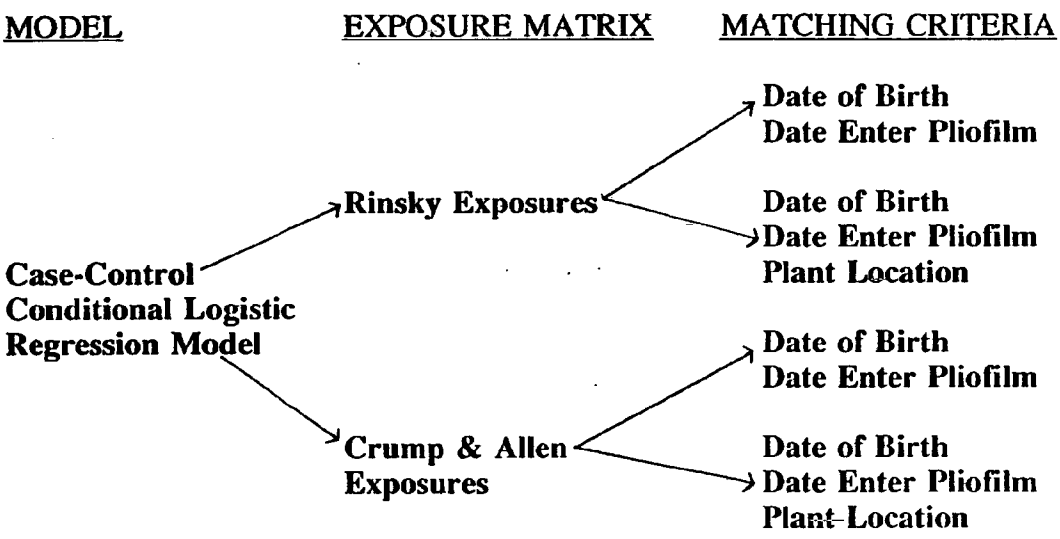
Rinsky et al. controls matched on:

- Date of birth
- Date of entering Pliofilm

ENVIRON controls matched on:

- Date of birth
- Date of entering Pliofilm
- Plant location

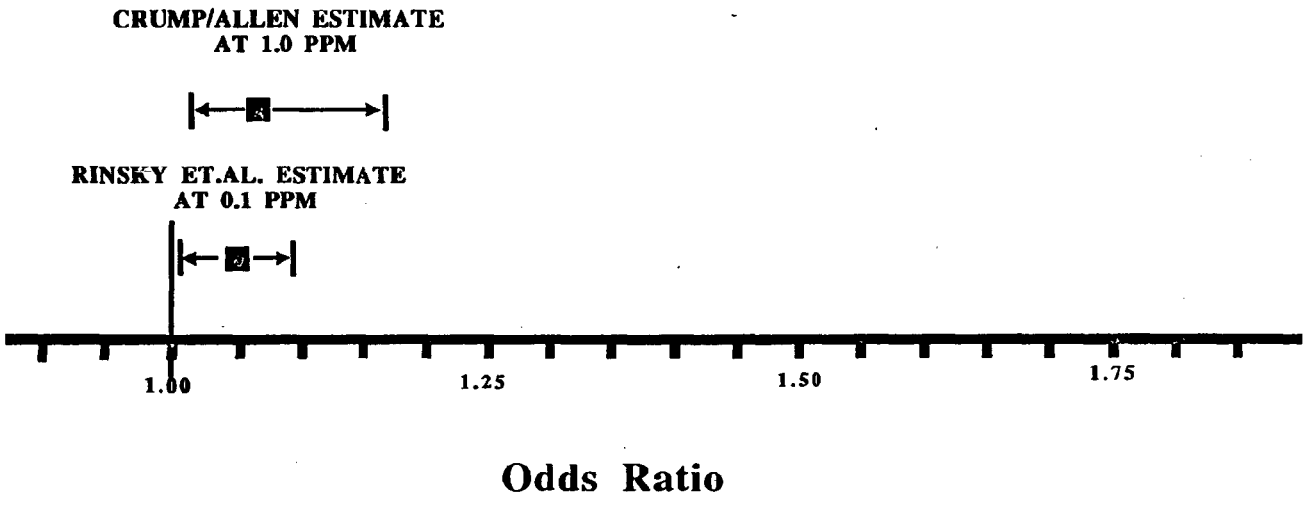
ENVIRON ANALYSIS



RESULTS OF ENVIRON ANALYSIS

RISKS ASSOCIATED WITH 40 YEARS OF BENZENE EXPOSURE IN WORKPLACE				
		Odds - Ratio		
Exposure Assumptions	Control Set Matching Criteria	0.1 ppm	1 ppm	10 ppm
Rinsky et al. (1987)	1 • Date of Birth • Date of entering Pliofilm	1.05	1.66	154.47
Rinsky et al. (1987)	2 • Date of Birth • Date of entering Pliofilm • Plant	1.04	1.53	69.41
Crump and Allen (1984)	(Same as 1 above)	1.01	1.07	1.97
Crump and Allen (1984)	(Same as 2 above)	1.01	1.07	1.97

CONFIDENCE LIMITS (95%) OF ODDS RATIOS FOR CRUMP/ALLEN AND RINSKY EXPOSURE ESTIMATES



Odds Ratio

RESULTS OF THE UPDATE

- In 1990 NIOSH completed an update of the Pliofilm cohort. This update extended the follow-up of the cohort from December 1981 through December 1988.
- API received a computer file of the information on the follow-up on March 20. This file is currently being analyzed.
- A preliminary scan of the file indicates that some additional cases of leukemia occurred during the 7 additional years of follow-up.

CONCLUSIONS

- Case-control conditional logistic regression model represents an improvement over prior models for benzene risk analysis because of maximal use of individual worker exposure data.
- Exposure estimation has most significant effect on risk estimates; matching on plant had relatively minor effect on risk.
- Odds ratios associated with a working lifetime of benzene exposure at 1 ppm, 8 hour TWA under Crump/Allen exposure estimates are not significantly different from those associated with a working lifetime of exposure at 0.1 ppm, 8 hour TWA under Rinsky et al. exposure assumptions.
- Because risk estimations are so sensitive to assumptions about exposure, there is a need to define more precisely the actual historical benzene exposures of this cohort.