The Carcinogenicity of Benzene and Public Health

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BRIEF EARLY HISTORY OF BENZENE TOXICITY: KEY DATES

1897 - SANTESSEN PUBLISHES FIRST LITERATURE REPORT OF CHRONIC BENZENE POISONING, OR APLASTIC ANEMIA. 4/9 YOUNG WOMEN WITH AA WORKING IN A BICYCLE FACTORY DIED WITHIN 1-4 MONTHS OF INITIAL EXPOSURE.

1928 - DELORE & BORGOMANO REPORT FIRST CASE OF LEUKEMIA RELATED TO BENZENE EXPOSURE -- OCCURRED IN ITALY (ALL)

1938 – PENATI & VIGLIANI REPORT AA WITH BONE MARROW HYPERPLASIA AND ACUTE AND CHRONIC LEUKEMIA

1971 - AKSOY BEGINS TO REPORT CASES OF APLASTIC ANEMIA AND LEUKEMIA AMONG TURKISH SHOE AND BOOT WORKERS USING SOLVENTS WITH HIGH BENZENE CONTENT; 14% OF APLASTIC ANEMIA CASES CONVERT TO AML

1976 - VIGLIANI REPORTS THERE ARE > 150 CASES OF BENZENE-LEUKEMIA IN LITERATURE; 17% OF AA CASES IN ITALIAN SHOE INDUSTRY CONVERTED TO AML

MORE RECENT HISTORY OF BENZENE TOXICITY: KEY DATES

AFTER ACCEPTANCE BY CLINICIANS THAT BENZENE WAS A KNOWN CAUSE OF LEUKEMIA, AUTHORITATIVE NATIONAL AND INTERNATIONAL ORGANIZATIONS HAD DIFFICULTY ACCEPTING THE EVIDENCE FROM TURKEY OR ITALY ….

1977 - INFANTE ET AL. PUBLISHE 5-10-FOLD RISK OF LEUKEMIA AMONG PLIOFILM RUBBER WORKERS EXPOSED TO BENZENE

ONLY AFTER THE **INFANTE ET AL. 1977** STUDY WAS BENZENE GENERALLY ACCEPTED AS A CAUSE OF AML.

1977 - OSHA ISSUES EMERGENCY TEMPORARY STANDARD FOR BENZENE 10→ 1 PPM

1987 – OSHA FINAL STANDARD DETERMINATION: SIGNIFICANT LEUKEMIA RISK AT 4.5 PPM-YEARS CUMULATIVE EXPOSURE (0.1 X 45 YEARS)

1982-2017 – QUANTITATIVE RISK ASSESSMENTS INDICATE THE "PLIOFILM STUDY" IS PROVIDING LEUKEMIA RISKS THAT ARE DIVERGENT FROM OTHER STUDIES

Pliofilm Cohort Revisited

Sources Used For Historical Review of Pliofilm Cohort

All publications of the Pliofilm cohort to date

Notes from NIOSH staff members who copied the employment records at the Goodyear facility (1976)

Records of the Pliofilm workers (both cohort and non-cohort members) categorized as deaths from leukemia, aplastic anemia, benzol poisoning, or other blood related disease while I was employed at NIOSH (1975-1978)

Personal notes and other documents from the conduct of the initial cohort follow-up

Correspondence with NIOSH Pliofilm investigators after 1978 while I was employed at OSHA

Testimony and other documents submitted to the OSHA Benzene Rulemaking Docket between 1976 and 1987, with particular reference to a report, testimony and cross examination and exhibits of Dr. Marvin Sakol, the treating hematologist for all but one of the blood disease patients identified during the study

News articles published in the Akron Beacon Journal during the time NIOSH was conducting its initial follow-up of the Pliofilm cohort (1976) –DETAILED REPORTING OF DIAGNOSES AND EXPOSURES FOR PLIOFILM LEUKEMIA CASES

Internal memoranda related to contract work for API benzene quantitative risk assessment;

Recently obtained Goodyear Tire and Rubber Company internal memoranda dated March 20, 1978

Leukemia Deaths That Occurred Between 1950-1964 Among White Males Who Worked in the AKRON Pliofilm Department

Year of Death	Age at Death	Cause of Death-ICD Code in Effect at Time of death	Treated by Dr. Sakol	Leukemia death #	Source ref #
		COUNTED LEUKEMIA DEATHS AMONG MEMBERS OF DEFINED COHORT			
1957	57	Acute monocytic leukemia (204.2)	-	1	Rinsky 2002
1958	60	Acute myelocytic leukemia (204.3)	+	2*	Rinsky 2002
1960	65	Acute myelogenous leukemia (204.3)	+	3	Rinsky 2002
1961	62	Di Guglielmo's acute myelocytic leukemia (204.3)	+	4*	Rinsky 2002
1961	57	Acute granulocytic leukemia (204.3)	+	5*W	Rinsky 2002
		"UNCOUNTED" LEUKEMIA DEATHS AMONG MEMBERS OF DEFINED COHORT			
1954	48	**AML changed to aplastic anemia** on discharge diagnosis so widow could receive worker's compensation; DC indicated an immediate cause of death as benzol poisoning-industrial (ICD-7 882)	+	6	Sakol 1977a Rinsky 1981
1961	51	**AML diagnosed by Dr. Sakol based on BM**, previous peripheral blood analysis indicated anemia and thrombocytopenia; DC indicated "pneumonia due to **hemorrhagic diathesis** (autopsy pending)" & coded (ICD-7 296); company physician had diagnosed him with heart disease and referred him to cardiologist	+	7	Balz 1976 Sakol 1977a Infante 1977 notes

Table 1 (continued)

Year of Death	Age at Death	Cause of Death-ICD Code in Effect at Time of death	Treated by Dr. Sakol	Leukemia death #	Source ref #
		"MORE UNCOUNTED" LEUKEMIA DEATHS FROM THE AKRON PLIOFILM OPERATION			
1963@	UK	AML Based on BM; No additional information	+	8	Sakol 1977a
UK@	UK	Leukemia—not able to locate family member to obtain permission to release name	+	9	Sakol 1977b
UK@	UK	Leukemia—hematologist threatened with law suit by family member still employed at Goodyear if name of patient released	+	10	Sakol 1977b

AML = acute myelogenous leukemia; UK = unknown, but likely diagnosed by 1963 (**Sakol 1977b**)
* = told by Company MD, they had "anemia;" @ = no medical records available from Goodyear

Source: Infante, PF (2013) Benzene and leukemia, Pliofilm revisited: I. An historical review of the leukemia deaths among Akron Goodyear Tire and Rubber Company employees. IJOEH 19: 215-222.

Excerpts From Testimony of Akron, Ohio Hematologist During OSHA 1977 Benzene Hearing

When he inquired in the late 1950s about chemical exposures in Pliofilm for workers who had quarterly blood tests, was informed BY COMPANY MD "**all chemicals had been tested and are non-toxic. The blood counts are just a routine thing to avoid government trouble" and "this is none of your business**."

Three workers whom he diagnosed with AML informed him they had considerable exposure in Pliofilm manufacturing to a substance called "**urbine**."

Was told by Company MD that urbine had been checked out and "**found to be entirely innocuous**," yet, the company code name for benzene was "urbine."

C.A Johnson, M.D., Corporate Medical Director, Goodyear Tire and Rubber Company, Internal Memorandum, March 29, 1978 – Pliofilm Deaths Due to Leukemia Between 1950-1969 Akron, Ohio

Cases No. 4, 6, 7 Not in NIOSH Study

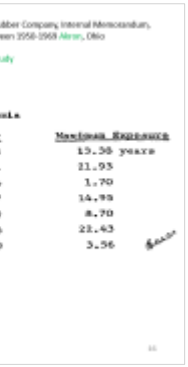


Table III

Deaths Due To Leukemia

Case	Age	Year	Maximum Exposure
1	60	1958	13.38 years
2	62	1961	21.93
3	82	1974	1.70
4	57	1957	14.95
5	65	1960	8.70
6	64	1966	22.43
7	58	1950	3.56

Summary of Estimated Unaccounted for Leukemia Deaths from Akron Only Portion of Pliofilm Cohort (N = 8)

Source	Number of leukemia deaths
Cohort member death changed from **AML to AA**	+1
Cohort member diagnosed by Dr. Sakol as AML (DC indicated **hemorrhagic diathesis**, autopsy pending, no final report)	+1
Sakol OSHA 1977 testimony he could not release names Of 3 Pliofilm workers he Dx with AML	+3
C. Johnson, MD, March 20, 1978 Goodyear internal memo (not identified by NIOSH of by Dr. Sakol)	+3
Estimated total missing leukemia deaths from Akron only	8

Leukemia Deaths Between 1950-1996 Among White Male Pliofilm Cohort Members Exposed to Benzene by Year and Age of Death and Plant Location

Year of Death	Age at Death	Cause of Death-ICD Code in Effect at Time of death	Plant Location	Leukemia death #
1950	29	Chronic myelogenous leukemia (204.1)	1	1
1954	28	Myelogenous leukemia "Chronic" (204.1)	1	2
1957	57	Acute monocytic leukemia (204.2)	2	3
1958	36	Monocytic leukemia (204.2)	1	4
1958	60	Acute myelocytic leukemia (204.3)	2	5
1960	65	Acute myelogenous leukemia (204.3)	2	6
1961	62	Di Guglielmo's acute myelocytic leukemia (204.3)	2	7
1961	57	Acute granulocytic leukemia (204.3)	2	8
1962-1978 (17 years)		**No leukemia deaths identified among cohort members**		
1979	67	Acute myeloblastic leukemia (205.0)	2	9
1984	67	Chronic myeloid leukemia (205.1)	2	10
1985	67	Acute lymphoid leukemia (204.0)	1	11
1985	67	Acute myeloid leukemia (205.0)	2	12
1986	71	Leukemia - unspecified (208.9)	1	13
1987	81	Leukemia - unspecified (208.9)	1	14
1991	79	Myeloid leukemia -unspecified (205.9)	1	15

Source: Adapted from Appendix Table A of **Rinsky et al. 2002;** 1 = St. Marys, Ohio; 2 = Akron, Ohio

Leukemia Deaths Between 1950-1996 Among White Male Pliofilm Cohort Members Exposed to Benzene (continued)

Year of Death	Age at Death	Cause of Death-ICD Code in Effect at Time of death	Plant Location	Leukemia death #
1976- NIOSH makes site visit and copies Pliofilm employment records				
1979	67	Acute myeloblastic leukemia (205.0)	2	9
1984	67	Chronic myeloid leukemia (205.1)	2	10
1985	67	Acute lymphoid leukemia (204.0)	1	11
1985	67	Acute myeloid leukemia (205.0)	2	12
1986	71	Leukemia - unspecified (208.9)	1	13
1987	81	Leukemia - unspecified (208.9)	1	14
1991	79	Myeloid leukemia -unspecified (205.9)	1	15

Source: Adapted from Appendix Table A of **Rinsky et al. 2002;** 1 = St. Marys, Ohio; 2 = Akron, Ohio

Observed and Expected Deaths from Leukemia Among Male and Female Pliofilm Workers (Entire Cohort by 3 Follow-up Periods)

Period of Followup	Number of Deaths			
	Observed	Expected	SMR	(95% CI)
SMR_1 1950-1961	8	0.59	13.55	(5.83-26.70)
SMR_2 **1962-1975**	**0**	**1.38**	**0.00**	
SMR_3 1976-1996	7	4.10	1.71	(0.69-3.52)

Source: **Silver et al. 2002, Appendix A**;

"ESTIMATED" LEUKEMIA DEATHS DURING YEARS 1962-1975 ASSUMING SAME RELATIVE RISK AS FOR PERIODS 1950-1961 and 1976-1996 SEPARATELY

SMR_2 1962-1975	"18.7"	1.38	13.55	(based on 1950 – 1961 SMR_1)
SMR_2 1962-1975	"2.4"	1.38	1.71	(based on 1976-1996 SMR_3)
Mid-point estimate:	"10.5"			

Note: Number in quotation is the estimated observed number of leukemia deaths for time period.

One Study Rarely Cited Indicating a risk of AML/leukemia in Line with Norwegian Off-shore Worker Studies

Talbott (2011) Risk of leukemia as a result of community exposure to gasoline vapors: A follow-up study. Environ Res 111, 597-602.

55,000 gallons of gasoline leak from petrol station storage tank and get into local sewage system

Residents begin smelling organic vapors in their homes ~ 1990

Cumulative benzene exposure to population:

Average = 0.03 ppm-years

Highest household = 2ppm-years

Exposures determined by **Pennsylvania Department of Health** and **Centers for Disease Control**

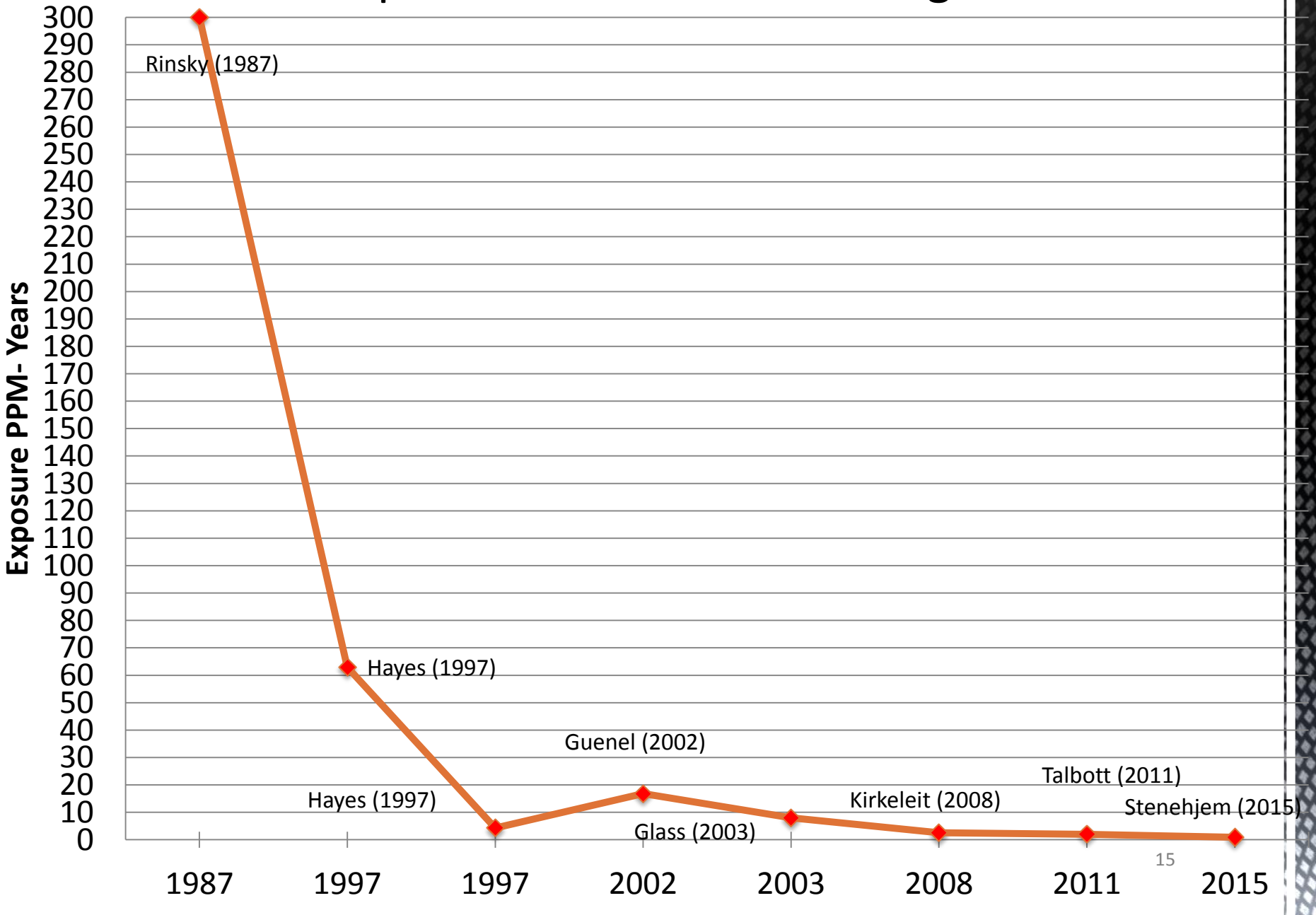
Age-Adjusted SIRs for total leukemia and AML in the combined gasoline spill areas of Hazle Township and Hazleton compared to Pennsylvania (PA) rates for three time intervals

	Total Leukemia				AML			
Intervals	**Obs**	**Exp**	**SIR**	**95% CI**	**Obs**	**Exp**	**SIR**	**95% CI**
1985-1989	0							
1990-1994	0	0.44	---	0-6.8	0	0.13	---	0-23.04
1995-2001	5	0.77	6.49*	2.1-15.1	3	0.26	11.5*	2.4-33.7

= $P < 0.05$

Source: Talbott (2011) Risk of leukemia as a result of community exposure to gasoline vapors: A follow-up study. Environ Res 111, 597-602.

Cum Bz Exp and Leukemia—Statis Sign Results



POPULATIONS INDICATING ELEVATED RISK FROM LOW CUMULATIVE BENZENE EXPOSURES

CUMULATIVE BENZENE EXPOSURE AND RELATIVE RISK OF LEUKEMIA

STUDY	OBS/EXP	RR	Exposure PPM-YRS.	LEUKEMIA TYPE
HAYES (1997)	10/3.1	3.2	**6.7** (< 10) *	MDS/AML
HAYES (1997)	7/2.6	2.7	**4.5** (< 40) #	MDS/AML
HEALTH WATCH	15/6.9	2.2	**< 4.9**	MYELOID
Signori Costantini (2003)	9/2.95	3.05	**14.7**	TOTAL LEUKEMIA
KIRKELEIT (2008)	6/2.08	2.89	**2.55 (max)** **0.81 (ave)**	AML

* = constant exposure group; California EPA, Office of Environmental Health Hazard Assessment (OEHHA) 2001

= cumulative exposure group

POPULATIONS INDICATING ELEVATED RISK FROM LOW CUMULATIVE BENZENE EXPOSURES (continued)

CUMULATIVE BENZENE EXPOSURE AND RELATIVE RISK OF LEUKEMIA

STUDY	OBS/EXP	RR	EXPOSURE PPM-YRS	LEUKEMIA TYPE
STENEJHEM (2015)	sign D-R	4.85	< 1	AML
		2.24	< 1	MYELOID
TALBOTT (2011)	5/1.20	6.49	**2 (max)** **0.03 (ave)**	TOTAL LEUKEMIA 1990-2001
TALBOTT (2011)	3/0.39	7.69	**2 (max)**	AML (1990-2001)
	3/0.26	11.54	**2 (max)** **0.03 (ave)**	AML (1995-2001)
	2/0.12	16.8	**Rel High**	AML (1990-2001)
GLASS (2003)	5	7.17	**12.04**	ANLL
	13	11.3	**11 – 23**	TOTAL LEUKEMIA
SCHNATTER (2012)	15	4.33	**> 2.93/<0.348**	MDS
	21	1.39	**> 2.93/<0.348**	AML

Will history repeat itself?

Will the delay in identifying benzene as a cause of AML prior to the Infante 1977 study be repeated today with benzene exposure and NHLs?

Evidence that benzene should be considered a known cause of NHL:

WHO has changed the definition of NHL to include a very broad range of lymphatic cancers

Epidemiological studies of NHL (including CLL, Myeloma and ALL in children) demonstrate significant association.

Previous debate now settled that myeloid and lymphoid cells are derived from same hematopoietic stem cell in which mutation leads to AML

Benzene affects multiple hematopoietic precursor chromosomal sites

Strong evidence in humans—benzene is genotoxic to lymphatic precursor cells

Dozens of papers showing genotoxic changes in circulating lymphocytes of benzene-exposed workers

Lymphomas observed in benzene-exposed laboratory animals in 10 separate studies

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Adapted from: Goldstein, BD. (2010) Benzene as a cause of lymphoproliferative disorders. Chemico-Biol Interactions 184, 147-150.

Significantly Elevated Risks of Childhood Leukemia Associated with the Following Sources of Benzene Exposure:

Gasoline

aromatic hydrocarbons from refinery pollution

petroleum waste sites

mobile sources (automobile exhaust)

Paints

paint products and thinners

secondary cigarette smoke in the home

Parental exposures to:

Benzene

Gasoline

motor vehicle related jobs

Painting

Home painting

Oil-based paints outside the home

rubber solvents

Mineral spirits.

Question? Do children represent a subpopulation that exhibits an elevated risk of leukemia from very low level environmental benzene exposure?

Sources: Carlos-Williams et al. (2015) Parental, In utero, and early-life exposure to benzene and the risk of childhood leukemia: A Meta-analysis. Am J Epid 183, 1-14. ; Infante, PF. (2017) Residential proximity to gasoline stations and risk of childhood leukemia. Am J Epid 185, 1-4. ; Steinmaus & Smith (2017) Response to "Proximity to gasoline stations and childhood leukemia." Am J Epid

CONCLUSIONS: BENZENE AND CANCER RISK

- **Conclusions on Benzene and Cancer Risk**

- The Pliofilm study should only be relied upon for hazard identification, not QRA

- Universal acceptance of data demonstrating benzene as a cause of AML was unnecessarily delayed for ~ 2 decades because of insufficient cohort study results.

- While the epidemiological data demonstrating significant positive associations with NHLs may be debatable, ...

- Mechanistic data demonstrating that benzene affects multiple hematopoietic stem cells, and is genotoxic to lymphatic precursor cells provide strong supporting evidence for benzene as a cause of human lymphoma.

- Although exposure-response relationship benzene and NHL is less well defined than for leukemia, reduction in benzene exposure will also reduce risk of human NHL

CONCLUSIONS: BENZENE AND CANCER RISK (continued)

- Direct observations from epidemiological study results demonstrating significantly elevated risks of AML/leukemia related to very low level exposures (~0.1 ppm) are also supported by ….
- Studies in both humans and animals demonstrating general cytotoxicity to granulocytes and genetic damage to these cells from similar exposure levels.
- Childhood leukemia associated with maternal exposure, and from multiple sources of environmental exposure suggest the potential for benzene-leukemia from low (ambient air) exposures in some situations (e.g., residential proximity to petrol stations).
- Responsible governmental bodies and the private sector should attempt to further reduce benzene exposures to the extent feasible.