IRIS Toxicological Review of Formaldehyde: New Science Summary for LHP Cancers

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June 2, 2010, EPA announced the release of the Draft Toxicological Review of Formaldehyde-Inhalation Assessment

USEPA 2010 Draft Formaldehyde IRIS Assessment

LHP Conclusions:

- *Weight-of-evidence analysis* – causal relationships between formaldehyde exposure and all LHP cancers as a group, all leukemias as a group and all myeloid leukemias as a group
- *Epidemiologic evidence* – considered supportive of a causal association between formaldehyde exposure and both Hodgkin lymphoma and multiple myeloma
- *Mode of action* – dependent upon hematological and genetic results reported by Zhang et al. (2010); results need to be extended and repeated
- *Dose-response assessment* – Beane-Freeman et al. (2009) judged to have exposure-response data adequate for the derivation of unit risk estimates

NAS 2011 Provides recommendations on Draft IRIS assessment relevant to LHPs

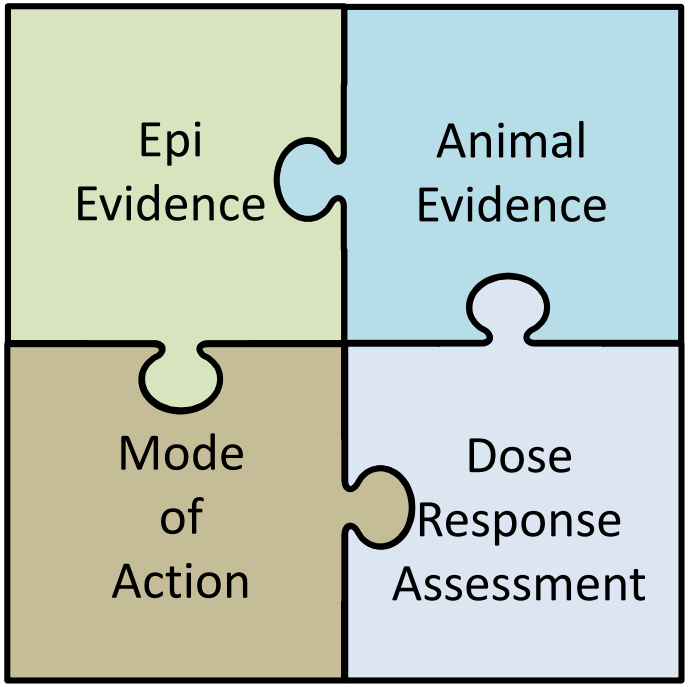
- **Animal Evidence**
  - Paucity of evidence for LHPs from animal models
- **Epidemiological Evidence**
  - Use specific diagnoses available
  - Re-evaluate peak vs. cumulative dose-metric
  - Define strengths, weaknesses, and inconsistencies of key studies
  - Justify use of Beane-Freeman et al. (2009)
- **Mode of Action**
  - Revisit arguments that support causality
  - Improve understanding of endogenous formaldehyde
  - Reconcile divergent statement regarding systemic delivery
  - data insufficient for cytogenetic effects at distant sites

NAS Recommendations relevant to LHPs (cont'd)

- **Quantitative Analyses**
  - Independent analysis needed
  - Alternative extrapolation models needed
  - BBDR modelling should be used
- **Evidence Integration**

  "EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version."

Integration of Evidence for LHPs



Lymphohematopoietic cancers - "…absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data."

New Animal Evidence
NAS Comment: Paucity of Evidence

- **Morgan et al. 2014**
  - No cases of leukemia or lymphohematopoietic neoplasia were seen. Formaldehyde inhalation did not cause leukemia in genetically predisposed C3B6.129F1-*Trp53*tm1Brd mice.
- **Morgan et al. 2015**
  - Formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice.
- *Attempts to publish these results have been unsuccessful; however, in an October 17, 2016 response to a letter from ACC urging publication of these reports, Dr. Linda Birnbaum stated, "All things considered, an NTP Research Report seems like a good solution."*

New Epidemiological Evidence

NAS Recommendation: Use specific diagnoses

- Checkoway *et al.* (2015) received original study data from NCI, verified original results of Beane Freeman *et al.* 2009 and conducted additional analyses that separated myeloid leukemias into acute myeloid leukemias (AMLs) and chronic myeloid leukemias (CML).
- Associations seen between formaldehyde exposure and Hodgkin lymphoma and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible.
- No other LHP malignancy was associated with either chronic or peak exposure to formaldehyde.

No excess mortality from AML or CML observed

	Checkoway et al. 2015				Beane Freeman et al. 2009			
	Non-exposed (n=3,136)		Exposed (n=22,483)		Non-exposed (n=3,108)		Exposed (n=22,511)	
	Obs	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
Myeloid leukemia	4	**0.69** (0.19-1.76)	44*	**0.86** (0.64-1.16)	4	**0.65** (0.35–1.74)	44	**0.90** (0.67–1.21)
AML	4	**0.93** (0.25-2.37)	30	**0.80** (0.56-1.14)	NR		NR	
CML	0		13	0.97 (0.56-1.67)	NR		NR	

US mortality rates used as the reference

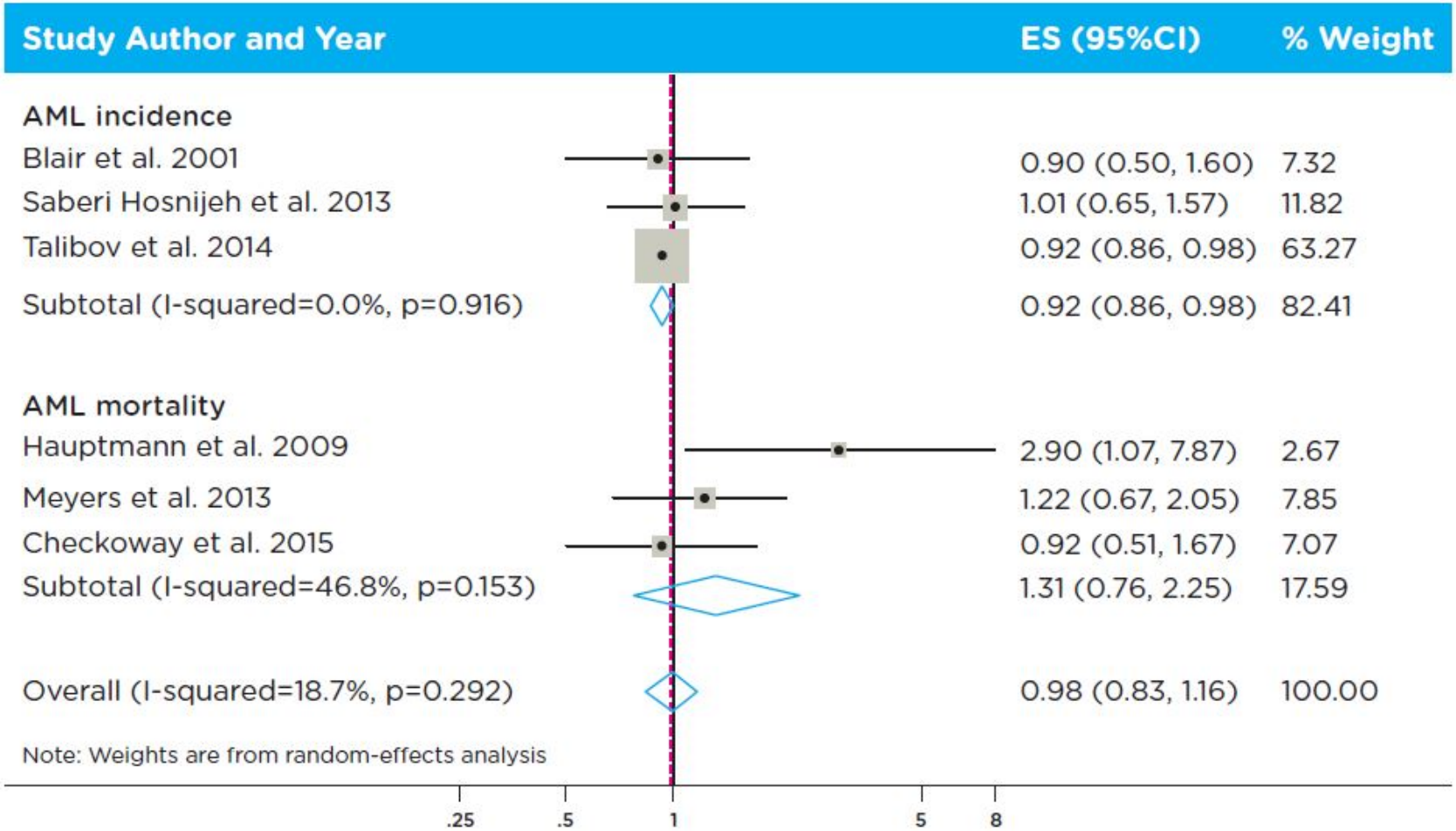
*One death was coded to ICD-8 205.9, unspecified myeloid leukemia.

Association between peak exposure and mortality from most specific diagnosis available (Checkoway et al. 2015)

	No peak		≥2.0 to < 4.0 ppm		≥4.0 ppm		
Diagnosis	**Obs**	**HR (95% CI)**	**Obs**	**HR (95% CI)**	**Obs**	**HR (95% CI)**	**P trend**
Hodgkin lymphoma	15	1.0 (referent)	5	2.18 (0.77-6.19)	7	3.38 (1.30-8.81)	0.01
Myeloid leukemia	27	1.0 (referent)	11	2.09 (1.03–4.26)	10	1.80 (0.85–3.79)	0.06
AML	**21**	**1.0 (referent)**	**7**	**1.71 (0.72–4.07)**	**6**	**1.43 (0.56–3.63)**	**0.31**
CML	**6**	**1.0 (referent)**	**3**	**2.62 (0.64–10.66)**	**4**	**3.07 (0.83–11.40)**	**0.07**

No increased risk of AML is seen in relation to occupational exposure to formaldehyde

AML studies stratified by incidence vs. mortality



New Epidemiological Evidence
NAS Comment: Re-evaluate peak vs. cumulative dose metric

- Checkoway *et al*. 2015 evaluated peak exposure and reported time since first and time since last peak exposure
  - Among the 13 of 34 AML deaths in the full cohort with peak exposures more than 2.0 ppm, only four worked in jobs with peaks within the 20 years preceding death
  - Only one AML death occurred (similar to expected) within the typical latency window of 2 to 15 years.

New Mode of Action Evidence

NAS Comment: Revisit arguments that support causality

- **Zhang et al. 2010**
  - reported significant changes* in blood parameters (WBC, lymphocyte, platelets, RBC counts) and increased frequency of aneuploidy in cultures of cells in vitro between exposed and unexposed workers.
- Conclusions:

  "…formaldehyde exposure can have an adverse effect on the hematopoietic system and that leukemia induction by formaldehyde is ***biologically plausible***, which heightens concerns about its leukemogenic potential from occupational and environmental exposures." (emphasis added)

*Actually, study was a cross-sectional design that reported differences in blood parameters between exposed workers and unexposed workers at one point in time. Changes in blood parameters over time were not investigated.

New Mode of Action Evidence

NAS Comment: Revisit arguments that support causality

- Gentry et al. (2013) re-analyzed data obtained via FOIA, **not including withheld individual exposure estimates**, suggesting other factors may have contributed to effects, which also may have arisen in vitro rather than in vivo.
  - significant methodological limitations identified (e.g., failure to follow study protocol) raised serious questions about whether this evidence provides support for a causal relationship between formaldehyde exposure and leukemia or lymphoid malignancies.

New Mode of Action Evidence

NAS Comment: Revisit arguments that support causality

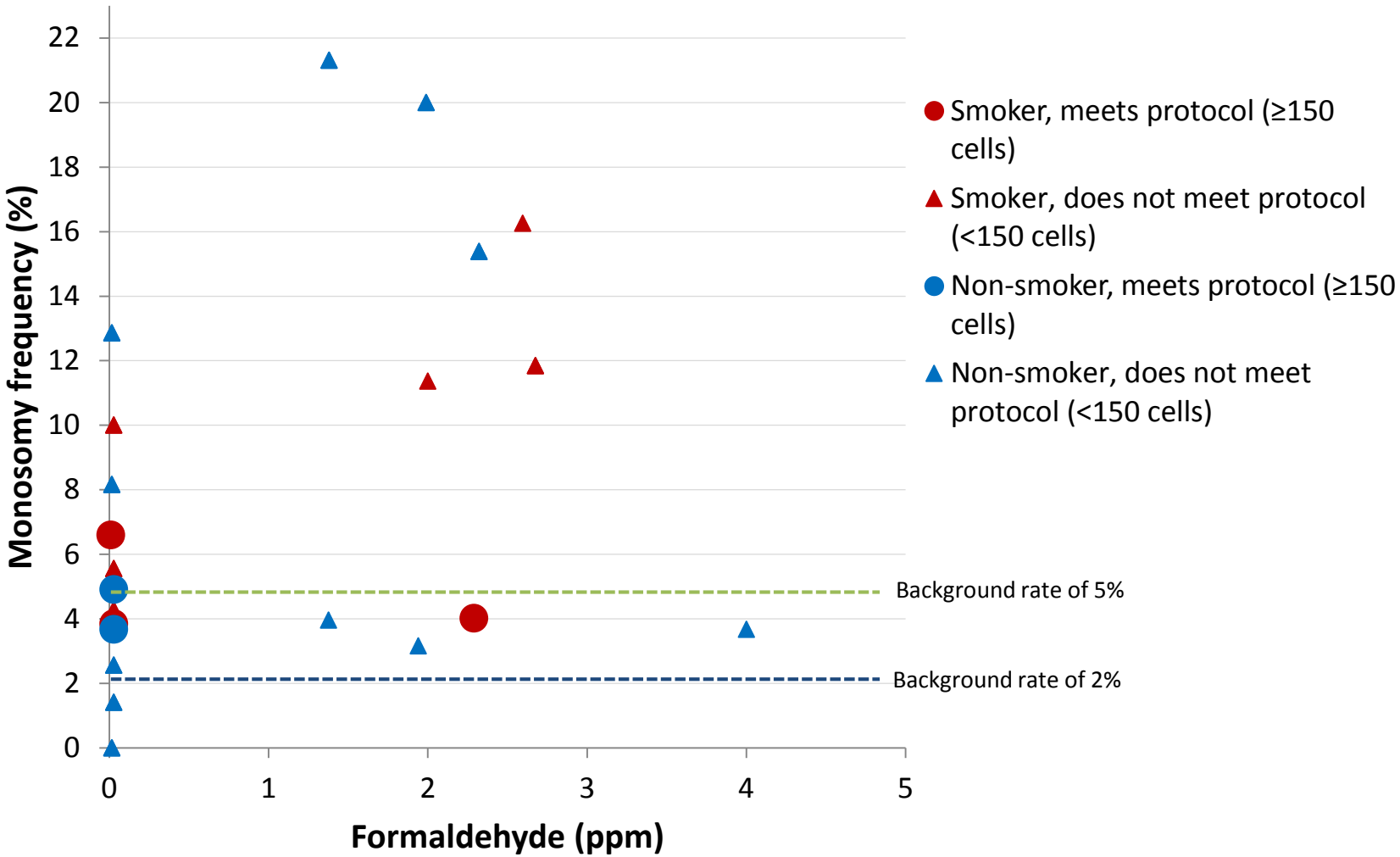
- Mundt et al. (submitted) re-analyzed FOIA data **including individual exposure data** obtained via DTA from NCI
  - *Comparing exposed to unexposed* – Analyses indicated few relationships between effects reported and formaldehyde exposure. The direction of some differences was opposite of what would be expected if caused by a toxic exposure.
  - *Correlation among exposed* – no correlation with formaldehyde exposure was seen for any parameter; sex and smoking were predictive of several differences in the blood measures.
  - Evaluation of aneuploidies – No relationship between formaldehyde exposure and monosomy 7 or trisomy 8 were seen – even assuming protocol had been followed properly.

Association between formaldehyde exposure and WBC and RBC counts and components

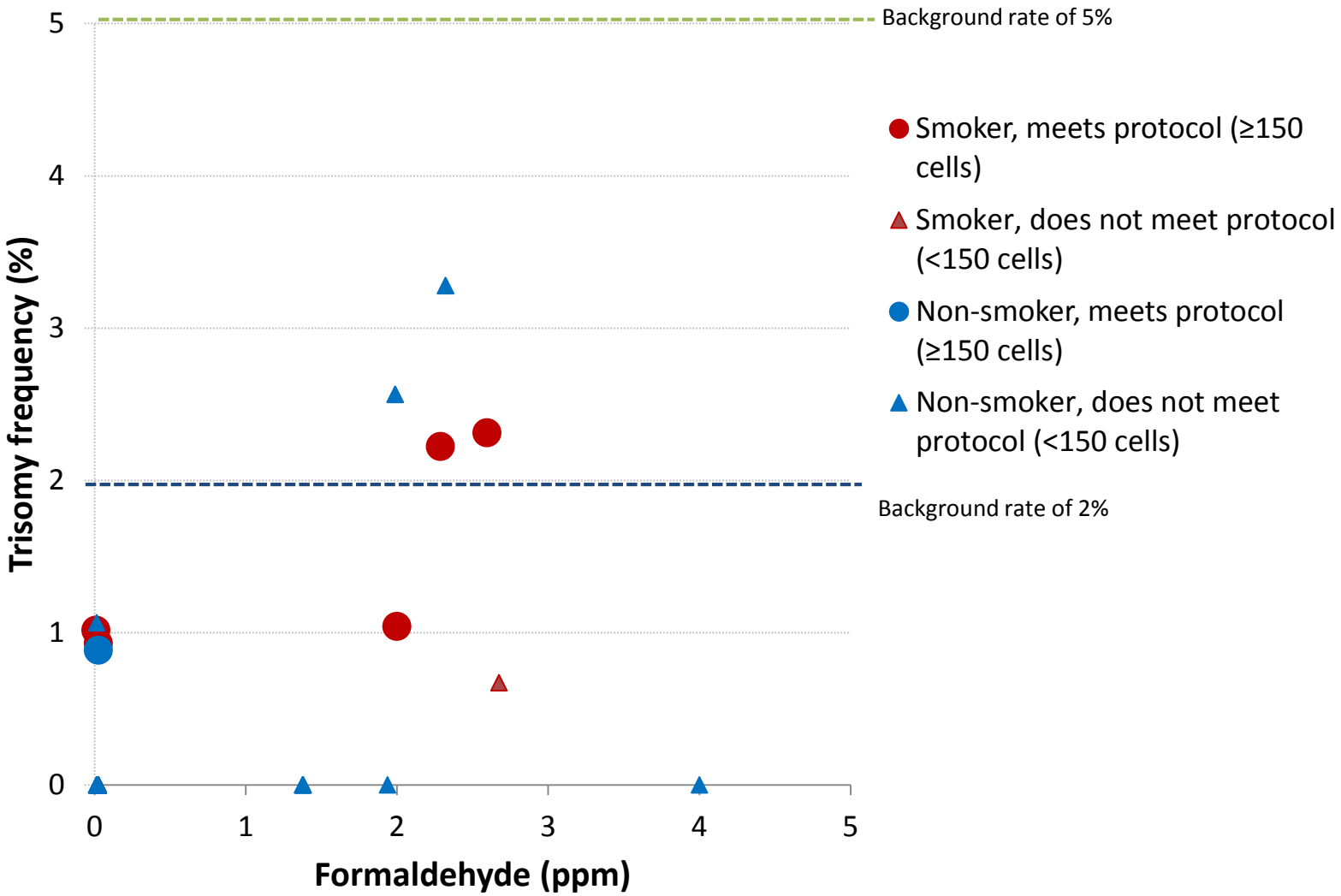
Exposure	Blood Count Adjusted RR	95% CI	†p-value	Blood Count Adjusted RR	95% CI	†p-value
	WBC			**RBC**		
Unexposed	1.00			1.00		
<1.3 ppm	***0.87**	0.78-0.97		***0.94**	0.91-0.98	
≥1.3 ppm	***0.85**	0.76-0.96	0.943	***0.94**	0.90-0.98	0.947
	Lymphocytes			**Hemoglobin**		
Unexposed	1.00			1.00		
<1.3 ppm	***0.85**	0.75-0.96		0.98	0.94-1.01	
≥1.3 ppm	***0.79**	0.69-0.90	0.660	0.99	0.95-1.03	0.818
	Monocytes			**MCV**		
Unexposed	1.00			1.00		
<1.3 ppm	0.90	0.77-1.06		1.03	0.99-1.08	
≥1.3 ppm	0.89	0.75-1.04	0.973	1.06	1.02-1.11	0.550
	Granulocytes			**Platelets**		
Unexposed	1.00			1.00		
<1.3 ppm	0.87	0.75-1.01		***0.85**	0.75-0.96	
≥1.3 ppm	0.88	0.75-1.03	0.997	0.91	0.80-1.03	0.674

†Comparison between exposed categories
*$p<0.05$ compared with unexposed

Monosomy 7


Monosomy frequency (%)
22
20
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4
5
Formaldehyde (ppm)
Background rate of 5%
Background rate of 2%
Smoker, meets protocol (≥150 cells)
Smoker, does not meet protocol (<150 cells)
Non-smoker, meets protocol (≥150 cells)
Non-smoker, does not meet protocol (<150 cells)

Trisomy 8


Background rate of 5%
Background rate of 2%
Smoker, meets protocol (≥150 cells)
Smoker, does not meet protocol (<150 cells)
Non-smoker, meets protocol (≥150 cells)
Non-smoker, does not meet protocol (<150 cells)
Trisomy frequency (%)
Formaldehyde (ppm)
0
1
2
3
4
5

Dose-Response Assessment

NAS Recommendation: Independent Analyses

- **Van Landingham et al. (2016)**
  - Using the original data from the key study (Beane Freeman et al. 2009), focused on duplication of the draft inhalation unit risk (IUR) and addressed comments from NAS regarding inputs and assumptions
- ***Conclusions***
  - *"Overall, documentation of the methods lacked sufficient detail to allow for replication of the unit risk estimates, specifically for Hodgkin lymphoma and leukemias, the key systemic endpoints selected by IRIS. The lack of apparent exposure-response relationships for selected endpoints, raises the question whether quantitative analyses are appropriate for these endpoints, and if so, how results are to be interpreted."*

Comparison of modelling statistics from Van Landingham et al. 2016 to statistics reported in USEPA (2010)

	Cox Regression	Logistic Regression			Poisson Regression		USEPA (2010)
	p-value [a]	R^2	LR p-value[b]	p-value [a]	LR p-value[b]	p-value [a]	p-value
Hodgkin lymphoma (201)	0.013	0.0133	0.098	0.019	0.09	0.037	0.06
Leukemia (204 – 207)	0.058	0.0017	0.35	0.055	0.003	<0.001	0.08
Leukemia (204 – 207, excluding 204.1)	0.239	0.0011	0.64	0.206	0.034	0.013	---
Acute myeloid leukemia (205.0)	0.844	0.0016	0.82	0.869	0.81	0.80	---

[a] p-values reflect the precision of any association between exposure and response, and show the probability that the beta value is not significantly different from zero. P-values < 0.05 indicate that the beta parameter is significantly different from zero.

[b] The likelihood ratio p-values of difference between a null and dose-dependent model (e.g. test of β=0) where small p-values reject the hypothesis that β=0. ..

Relative risk for Hodgkin lymphoma based on peak exposure from Poisson model stratified by calendar year, age, sex, and race and adjusted for pay category

				Van Landingham et al. 2016		Beane Freeman et al. 2009	
	Subjects	Person-years	Deaths	RR	CI	RR	CI
0	3,139	104,386	2	**3.32**	0.60-18.26	**0.67**	0.12-3.60
0 to 2	10,302	415,987	6	**1.0**	Referent	**1.0**	Referent
2 to 4	6,010	254,723	8	**0.76**	0.30-1.89	**3.30**	1.04-10.50
≥4 ppm	6,198	256,618	11	**2.96**	0.94-9.27	**3.96**	1.31-12.02

p trend[1] (reported by Beane Freeman)		0.01
p trend[2] (reported by Beane Freeman)		0.004
log likelihood (reported by Van Landingham)	-309.87	
p-value[3] (reported by Van Landingham)	0.04	

[1]Two-sided likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure among exposed person-years only.
[2] Two-sided likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years.
[3] Two-sided likelihood ratio test

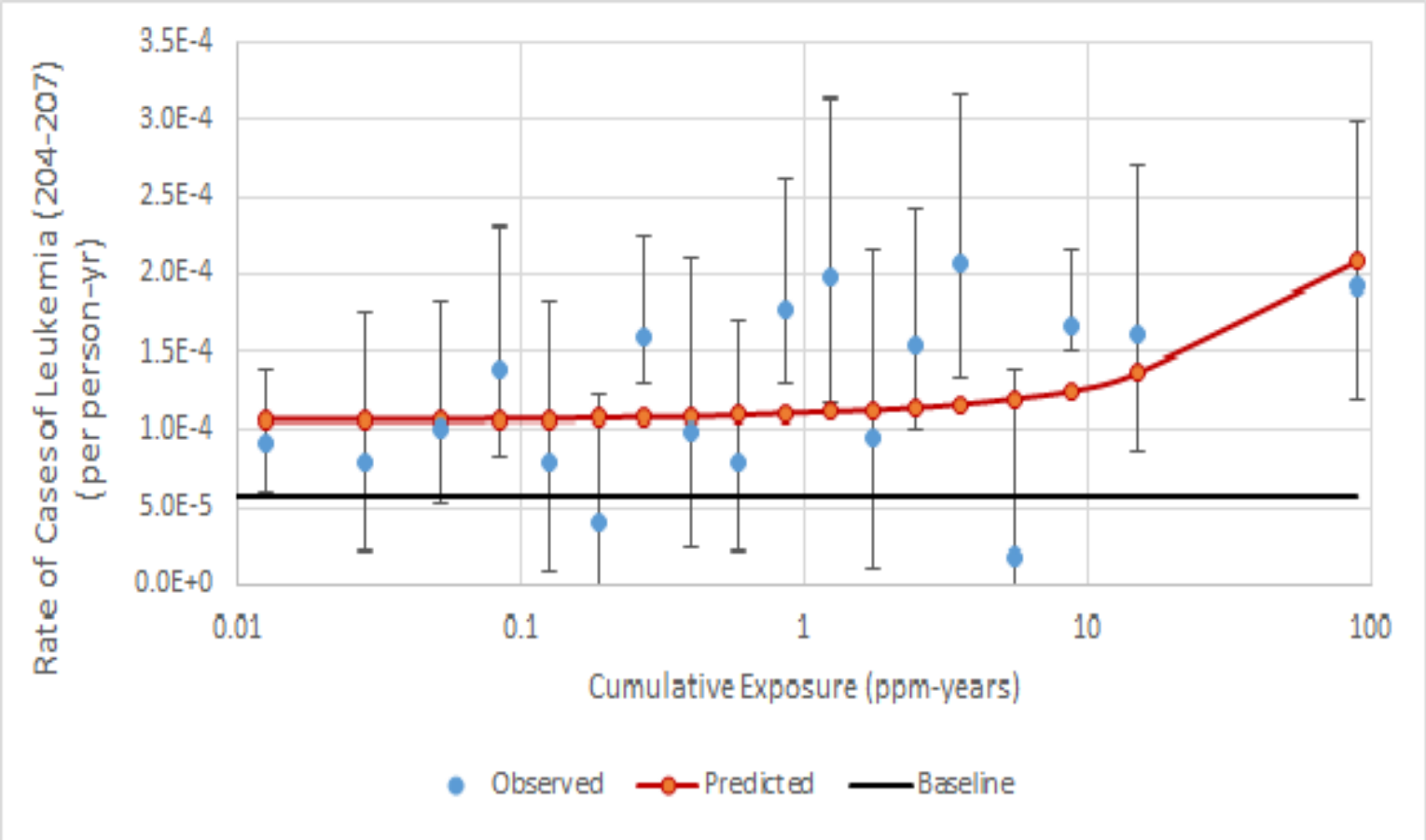
Relative risk for all leukemias based on peak exposure from Poisson model stratified by calendar year, age, sex, and race and adjusted for pay category

				Van Landingham et al. 2016		Beane Freeman et al. 2009	
	Subjects	Person-years	Deaths	RR	CI	RR	CI
0	3,139	104,386	2	**1.83**	0.76-4.40	**0.59**	0.25-1.36
0 to 2	10,302	415,987	6	**1.0**	Referent	**1.0**	Referent
2 to 4	6,010	254,723	8	**0.58**	0.36-0.93	**0.98**	0.60-1.62
≥4 ppm	6,198	256,618	11	**1.07**	0.66-1.75	**1.42**	0.92-2.18

p trend[1] (reported by Beane Freeman)		0.12
p trend[2] (reported by Beane Freeman)		0.02
log likelihood (reported by Van Landingham)	-1177.94	
p-value[3] (reported by Van Landingham)	0.004	

[1]Two-sided likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure among exposed person-years only.
[2] Two-sided likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years.
[3] p-value for the likelihood ratio chi square test

Comparison of Estimated Cases from the Poisson Regression model to number of cases of Leukemias Observed at the end of follow-up period in the Beane Freeman et al. (2009) study. Observed and Predicted Results Over Full Observed Exposure Range

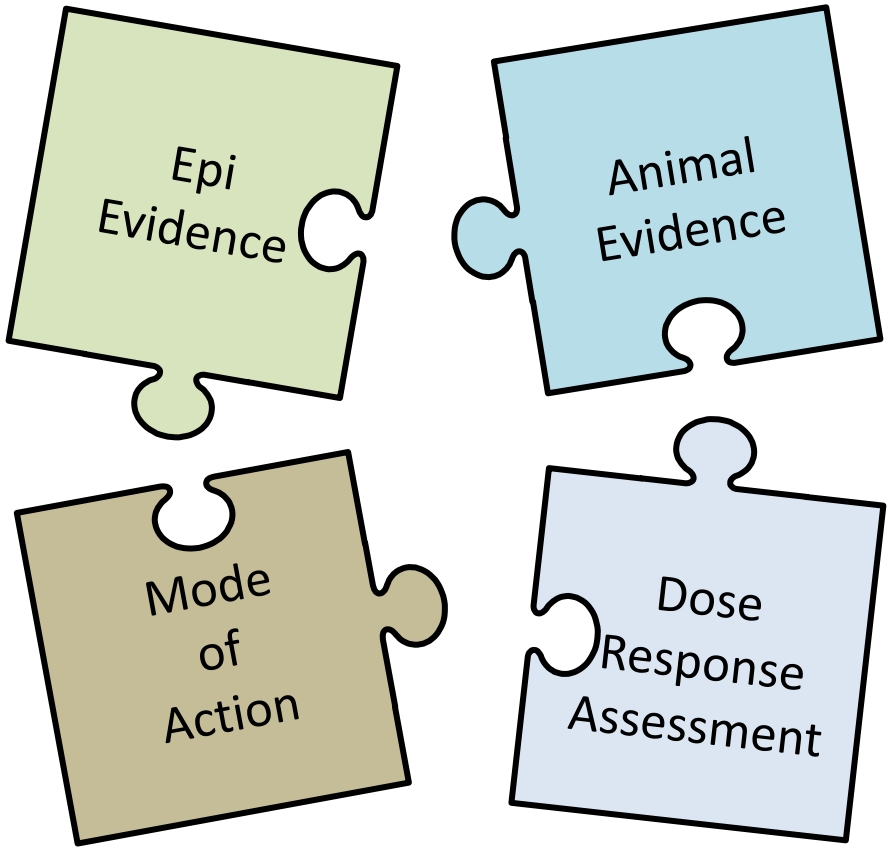


Dose-Response Assessment

NAS Recommendation: Independent Analyses

- **Van Landingham et al. 2016**
  - Large variability in the low dose region which is poorly fit by models
  - Unable to reproduce the Beta values reported in USEPA (2010)
  - Inconsistencies between life table instructions in USEPA (2010) and life table results reported

NAS 2011 Comments/Data Gaps



Addressing the NAS Comments provides increasing evidence of a lack of a causal association between formaldehyde exposure and lymphohematopoietic cancers

New Animal Evidence

NAS Recommendation	Addressed by
Data gap: Paucity of evidence for LHP from animal models	**Morgan et al. (2015)** • No cases of leukemia or lymphohematopoietic neoplasia were seen. Formaldehyde inhalation did not cause leukemia in genetically predisposed C3B6.129F1-Trp53tm1Brd mice. **Morgan et al. (2014)** • Formaldehyde inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice.

New Epidemiological Evidence

NAS Recommendation	Addressed by
Define strengths, weaknesses, and inconsistencies of key studies	**Checkoway et al. 2012** • A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoetic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation.
Use specific diagnoses available	**Checkoway et al. 2015** • New analyses of the NCI formaldehyde workers cohort specifically for AML are reported. Results do not support the hypothesis that formaldehyde causes AML. • Associations seen between formaldehyde exposure and Hodgkin leukemia and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. **Boffetta et al. 2016** • Some prominent recent evaluations have concluded that formaldehyde is leukemogenic, especially for the myeloid types1,12. • However, overall evidence from studies specifically examining occupational exposure to formaldehyde and AML demonstrates no clear or consistent increased risk of AML. The meta-RR estimates are not statistically significantly elevated, and the null findings were tolerant to various sensitivity tests, including omitting the most influential study. • Given the lack of animal studies demonstrating leukemogenicity, a lack of direct evidence for a mode of action and compelling new experimental evidence that formaldehyde is incapable of reaching bone marrow13, the absence of any clearly or convincingly increased meta-RR adds to the growing body of evidence indicating that formaldehyde exposure is unlikely to cause AML.

New Epidemiological Evidence

NAS Recommendation	Addressed by
Re-evaluate peak vs. cumulative dose-metric	**Checkoway et al. 2015** • Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure. • Few deaths occurred within 20+ years of last peak exposure. • Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (Ptrend= 0.05) and peak (Ptrend = 0.003) exposures. • Suggestive associations with peak exposure observed for chronic myeloid leukemia, based on very small numbers. • No other lymphohematopoietic malignancy was associated with either chronic or peak exposure.
Justify use of Beane-Freeman et al	**Meyers et al. 2013** • Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results demonstrated limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases. **Coggon et al. 2014** • Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941-2012. Results provide no support for an increased hazard of myeloid leukemia from formaldehyde exposure.

New Mode of Action Evidence (1)

NAS Recommendation	Addressed by
Data gap: Improve understanding of endogenous formaldehyde	**Schroeter et al. 2014** • Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations. **Yu et al. 2015** • With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively.
Reconcile divergent statement regarding systemic delivery	**Yu et al 2015; Edrissi et al. 2013; Moeller et al. 2011; Lu et al. 2011** • Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact.

New Mode of Action Evidence (2)

NAS Recommendation	Addressed by
Revisit arguments that support causality	**Gentry et al. 2013** • Reanalysis of selected raw data from the Zhang et al. (2010) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect in vivo events, the reanalysis of the results provided by Zhang et al. (2010) raise sufficient questions that limit the use of Zhang et al. (2010) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. **Mundt et al. 2016 (submitted for publication)** • Reanalysis of raw data from Zhang et al. (2010) including exposure data. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts are not exposure-dependent. Among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk.

New Mode of Action Evidence (3)

NAS Recommendation	Addressed by
Data gap: data insufficient for cytogenetic effects at distant sites	**Albertini et al. 2016** • Critical review of the genotoxicity literature found no convincing evidence that exogenous exposures to FA alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically not in the bone marrow. • Review of the existing studies of hematotoxicity, likewise, failed to demonstrate myelotoxicity in any species– a probable prerequisite for leukemogenesis.

New Dose-Response Assessments (1)

NAS Recommendation	Addressed by
Independent analysis needed	**Van Landingham et al. 2016** • The documentation of the methods applied in the USEPA (2010) IRIS document lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the Beane Freeman et al. (2010). This lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints.
Alternative extrapolation models needed	**Starr and Swenberg 2013** • Results of the "Bottom-up " approach indicate that recent top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. **Starr and Swenberg 2016** • Updated "Bottom-Up" risk estimates heighten the marked contrasts that are present between the previous estimates and the corresponding USEPA estimates, with the larger difference for leukemia being due primarily to the significantly improved detection limit for the analytical method used in quantitating DNA adduct numbers.

New Dose-Response Assessments (2)

NAS Recommendation	Addressed by
BBDR modelling should be used	**Clewell H, et al. (in preparation)** • Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. **Gentry PR, et al. (in preparation)** • Review of the utility of BBDR modeling for use in risk assessment focusing primarily on the use of BBDR modeling in predicting the human health risk of formaldehyde exposure. This review addresses the current published criticisms for BBDR modeling use in risk assessment, and highlights the advantages of expanding the application of BBDR modeling in risk assessment.

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