Combining data within species: Meta-analysis in IRIS

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Introduction

Often, human health risk assessments have relied on qualitative approaches for hazard identification, which involves weight of evidence determinations that integrate evidence across multiple studies. In 2014, the National Research Council recommended that IRIS develop and apply quantitative approaches for evidence integration, including the application of meta-analyses to animal and human data, to help summarize and evaluate the results of a systematic review. In the meta-analytic approach, a pooled effect size is calculated after consideration of multiple potential confounding factors in order to determine whether the entire database under consideration indicates a chemical is a hazard. Two examples demonstrate approaches used in IRIS assessments: TMB (trimethylbenzene) neurotoxic hazard and pleural plaques effect on lung function.

Trimethylbenzene and pain sensitivity: methods

- A publically available, comprehensive literature search was performed in support of the IRIS Toxicological Review of trimethylbenzenes (TMBs)
- Six neurotoxicity studies were found that investigated decreased pain sensitivity following exposure in individual TMB isomers or a mixture thereof (i.e., C-9 fraction) - studies differed in testing time, test agent, and application of foot shock
- Qualitative hazard identification concluded the pain sensitivity was a hazard and that testing time mainly influenced observation of effect
- Methods outlined in Vesterinen et al. (2014) and Viechtbauer (2010) were applied using the Metafor R package
  - Random and mixed-effects models were run
  - Effect sizes were calculated as standardized mean differences
  - Hedge's G was used to account for bias due to small sample sizes
  - Restricted maximum likelihood was used to calculate total heterogeneity to prevent underestimated/biased estimates of variance
  - Publication bias, normality of residuals and sensitivity analyses were investigated

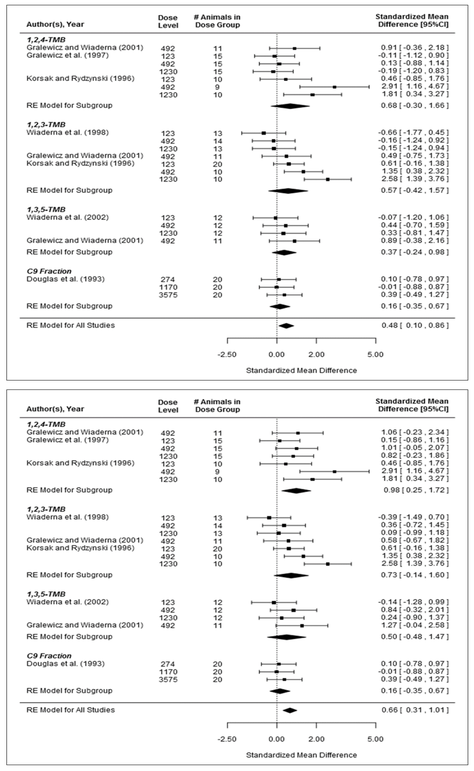


Figure 1. Forest plots for pain sensitivity studies. (A) Pre-foot shock; (B) post-foot shock

Trimethylbenzene and pain sensitivity: results

Table 1– Meta-regression results for TMB and mixture studies included in analysis

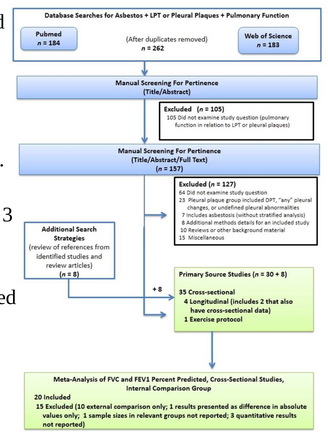
Moderating Variable	Effect Size (95% CI) Model 1	Model 2	Number of Animals	Number of Groups	Adjusted R^2	Q_E p-value[a]	Q_M p-value[b]
Pre-Foot Shock Results							
Pooled Estimate	0.479 (0.103-0.855)		283	21			
Lab							
Nofer	0.550 (0.129-0.971)*	Ref	223	18	0.0%	0.006	0.423
Douglas	0.159 (-0.751-1.069)	-0.392 (-1.394-0.610)	60	3			
Testing Time							
0 days	1.331 (0.813-1.849)***	Ref	69	6	93.9%	0.333	0.002
1 day	0.158 (-0.424-0.740)	-1.173 (-1.95.2- -0.394)**	60	3			
50 days	0.106 (-0.258-0.470)	-1.225 (-1.858- -0.591)***	154	12			
Isomer							
1,2,4-TMB	0.647 (-0.099-1.393)	Ref	85	7	0.0%	0.003	0.845
1,2,3-TMB	0.573 (-0.121-1.266)	-0.074 (-1.093-0.944)	91	7			
1,3,5-TMB	0.386 (-0.575-1.346)	-0.261 (-1.477-0.955)	47	4			
C9 fraction	0.159 (-0.828-1.145)	-0.488 (-1.725-0.749	60	3			
Dose	0.0001 (-0.0004-0.0006) for each 10 mg/m^3 increase				0.0%	0.004	0.718
Post-foot Shock Results							
Pooled Estimate	0.663 (0.314-1.012)		283	21			
Lab							
Nofer	0.772 (0.397-1.146)***	Ref	223	18	22.02%	0.041	0.153
Douglas	0.159 (-0.619-0.936)	-0.613 (-1.476-0.250)	60	3			
Foot-shock							
Yes	0.911 (0.395-1.426)**	Ref			0.00%	0.024	0.196
No	0.467 (0.004-0.929)*	-0.444 (-1.137-0.249)					
Testing Time							
0 days	1.361 (0.812-1.909)***	Ref	69	6	72.65%	0.238	0.013
1 day	0.158 (-0.467-0.784)	-1.203 (-2.034- -0.371)**	60	3			
51 days	0.459 (0.074-0.844)*	-0.902 (-1.572- -0.232)*	154	12			
Isomer							
1,2,4-TMB	1.004 (0.346-1.662)**	Ref	85	7	0.0%	0.030	0.410
1,2,3-TMB	0.722 (0.128-1.316)*	-0.282 (-1.168-0.604)	91	7			
1,3,5-TMB	0.5.5 (-0.330-1.361)	-0.489 (-1.560-0.582)	47	4			
C9 fraction	0.159 (-0.665-0.982)	-0.846 (-1.900-0.209)	60	3			
Dose	0.0001 (-0.0004-0.0005) for each 10 mg/m^3 increase				0.0%		0.807

Model 1 – Intercept suppressed, effects estimated separately for each variable level; Model 2 – estimated effects are relative to the variable level identified as the Reference.
Individual categorical moderators are statistically significant at the following levels: * p < 0.05; ** p < 0.01; *** p < 0.001
[a] Q_E is the test for residual heterogeneity; p-values < 0.05 possibly indicate that other moderators not included in the model may influence the measured outcome, specific to Model 2
[b] Q_M is the omnibus test of moderators; p-values < 0.05 indicate that the moderators included in the model have a significant influence on the measured outcome, specific to Model 2

- Quantitative meta-analyses and meta-regressions supported original qualitative hazard identification determination – ***decreased pain sensitivity is a hazard in humans following exposure to trimethylbenzene isomers***
- Time of testing appeared to be the study-level variable that most strongly affected differing study results and explained the majority of inter-study heterogeneity

Pleural plaques effect on lung function: methods

A literature search was conducted using the PubMed and Web of Science databases with no publication date limitations. Studies were excluded if
- the plaques group included individuals with diffuse pleural thickening (DPT)
- undefined pleural or parenchymal abnormalities.



Each paper was reviewed independently by 2 of the 3 reviewers. In cases of disagreements, the 3rd reviewer reviewed the paper and participated in the consensus- building discussions. Reviewers evaluated potential limitations in 5 aspects of study design:
- selection of participants
- protocols for x ray or HRCT readings
- protocols for spirometry measurements;
- analytic approach
- considerations of smoking.

The Metaphor R package was used for the meta-analyses
- A random effects model was used for both FVC and FEV1
- To assess possible publication bias, funnel plots were evaluated. Additional sensitivity analyses were conducted to evaluate the potential effect of identified limitations on the meta-analyses results.

Pleural plaques effects on lung function: results

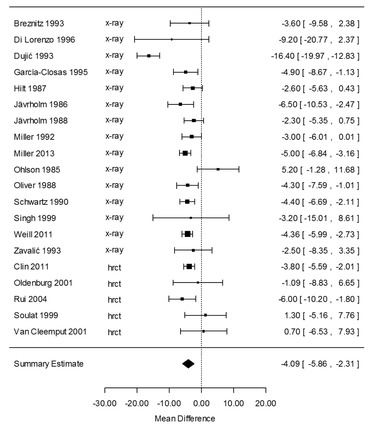


Figure 1 (FVC)

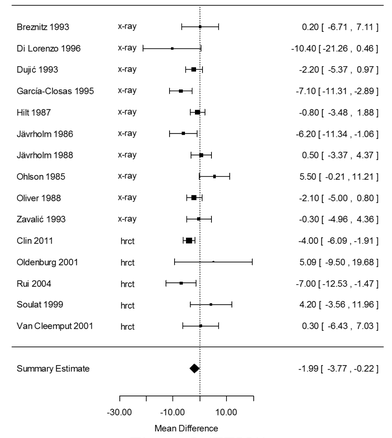


Figure 2 (FEV1)

- The summary effect estimates for both FVC and FEV1 are statistically significant, showing a change of −4.09 %pred (95% CI: −5.86, −2.31) and −1.99 %pred (95% CI: −3.77, −0.22), respectively (See Fig. 1 and Fig. 2)
- The results of larger studies are very consistent in showing a decrease in FVC (see Fig. 1). In contrast, fewer large studies are available for FEV1, and there is less consistency in the results (see Fig. 2).
- At the individual level, the decrement in FVC or FEV1 may or may not be noticeable for a given patient; while many with pleural plaques could have well-preserved lung function, there are some at the lower end of 'normal' lung function, for whom even a small additional decrement would result in an increased in disease severity (e.g., mild to moderate disease).
- At the population level, even small changes in the average of a distribution of lung function can result in a proportion of the exposed population shifted down into the lower "tail" of the distribution, into clinically significant lung function deficit region

Discussion

- Both human and animal data are amenable to quantitative synthesis via meta-analysis
- Studies need not be exactly the same, as long as results are reported in a consistent way or can be converted into a comparable format (e.g., use of standardized mean difference as effect metric)
- Use of free R software allows conducting meta-analysis
- Use of meta-analytic methods for hazard identification are in line with National Research Council (2014) recommendations for the development of quantitative hazard identification and evidence integration methods
- Applying meta-analysis and meta-regression methods will help to improve future risk assessments and ensure the use of the best available science

References:

Davis JA, Kraft A. Quantitative meta-analytic approaches for the systematic synthesis of data and hazard identification: a case study of decreased pain sensitivity due to trimethylbenzene exposure. 2017. *Environmental Research.* 158: 598-609.

Kopylev L, Christensen KY, Brown JS, Cooper GS. A systematic review of the association between pleural plaques and changes in lung function. 2015. *Occupational and Environmental Medicine.* 72(8): 606-14.