PREGNANCY OUTCOME FOLLOWING MATERNAL ORGANIC SOLVENT EXPOSURE: A META-ANALYSIS OF EPIDEMIOLOGICAL STUDIES

by

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A thesis submitted in conformity with the requirements
for the degree of M.Sc.
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ABSTRACT

Pregnancy Outcome Following Maternal Organic Solvent Exposure: A Meta-Analysis of Epidemiological Studies

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Evidence of fetal damage or demise from organic solvent levels that are not toxic to the pregnant woman is inconsistent in the medical literature. The risk for major malformations and spontaneous abortion from maternal inhalational organic solvent exposure during pregnancy was summarized using meta-analysis. Medline, Toxline and Dissertation Abstracts databases were utilized to search for all research papers published in any language from 1966 to 1994. Included were studies that were case-control or cohort in design and indicated first trimester (or up to 20 weeks gestation for spontaneous abortion) maternal solvent exposure. Research results were combined by the Mantel and Haenszel method. In total, 559 studies were obtained from the literature search. Five studies for each outcome of interest were included into the analysis. The overall summary odds ratio (ORs) for major malformations was 1.64 with a 95% CI of 1.16-2.30. The ORs for spontaneous abortion was 1.25 with a 95% CI of 0.99-1.58. These results indicate that maternal inhalational occupational exposure to organic solvents is not associated with an increased risk for spontaneous abortion. However, the significance of the results with regard to malformations warrants further investigation.

ACKNOWLEDGEMENT

I would like to acknowledge...

My supervisor, Dr. Gideon Koren, for his continuous guidance, assistance and encouragement through my project.

My Advisor, Dr. Neal Shear, who provided me with additional ideas and direction.

Dr. Thomas Einarson for his expertise in the area of statistics and the technique of meta-analysis and for his continual patience and support during this study.

Ernest Kopecky and Merry Chu who were the judges for the meta-analysis and who spent many hours reading and rating the literature selected.

Imperial Oil Limited for the generous funding of this project.

My fellow graduate students who provided endless advice, encouragement, and comic relief - Merry, Myla, Edith, Paul and last but definitely not least, Nathalie.

My parents who tolerated my work habits and who helped me in ways that they will never know. To say thank you will never be enough.

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INTRODUCTION

REVIEW OF PROBLEM

Teratology, the study of environmentally induced birth defects, developed into a modern science in the mid 1900's when Gregg demonstrated in 1941 that maternal infection with the rubella virus was capable of causing malformations in humans. It became evident that the conceptus is subjected to a variety of environmental influences which may have deleterious effects upon its development. As an example, organic solvent exposure during pregnancy yields a rich literature background (1-576)

Organic solvents are a structurally diverse group of low molecular weight liquids that are able to dissolve other organic substances (576). Chemicals in the solvent class include aliphatic hydrocarbons (mineral spirits, varnish, kerosene); aromatic hydrocarbons (benzene, toluene, xylene); halogenated hydrocarbons (carbon tetrachloride, trichloroethylene); aliphatic alcohols (methanol); glycols (ethylene glycol); and glycol ethers (methoxyethanol). Fuels are a mixture of various hydrocarbons. They are generally ubiquitous in industrialized society, both at work and at the home. They may be encountered as individual agents or in complex mixtures such as gasoline. Incidental exposures may include vapors from gasoline, lighter fluid, spot removers, aerosol sprays and paints. These short duration and low level exposures may often go undetected. More serious exposures occur mainly in the industrial or laboratory settings during manufacturing and processing operations such as dry cleaning, regular working with paint removers, thinners, floor and tile cleaners, glue and as laboratory reagents. Gasoline sniffing or glue sniffing, albeit not occurring in the occupational setting, is another source of exposure to organic solvents during pregnancy.

Counseling pregnant women who are occupationally exposed to numerous chemicals (mostly organic solvents) is difficult because it is hard to estimate the

predominant chemicals and their by-products. Even after identifying the more toxic agents, it is still difficult to asses the circumstances of exposure as for many chemicals one can measure neither airborne nor blood levels. Smelling the odor of organic solvents is not indicative of a significant exposure as the olfactory nerve can detect levels as low as several parts per million which are not necessarily associated with toxicity. As an example, the odor threshold of toluene is 0.8 parts per million whereas the TLV-TWA (threshold limit value-time weighted average) is 100 parts per million. In addition, reproductive information on many individual solvents is at best sparse, either limited to animal studies or nonexistent.

Many organic solvents are teratogenic and embryotoxic in laboratory animals depending on the specific solvent, dose, route of administration and particular animal species (576). The various malformations described include hydrocephaly, exencephaly, skeletal defects, cardiovascular abnormalities and blood changes. Also, some studies suggest poor fetal development and neurodevelopmental deficits. In a portion of these studies exposure levels were high enough to induce maternal toxicity.

Organic solvents are a diverse, complex group and because exposure usually involves more than one agent and different circumstances, adequate human epidemiological studies are difficult to interpret. Many studies are subject to recall and response bias and are not always controlled for other risk factors such as age, smoking, ethanol, and concurrent drug ingestion. It is hard to prove or quantitate the suspicion that organic solvents are a reproductive hazard. One may even expect that a ubiquitous exposure to solvents would by chance alone be associated with an increase in birth defects or spontaneous abortions, which may differ from one study to another. While fetal toxicity is biologically sensible in cases of intoxicated mothers, evidence of fetal damage from levels that are not toxic to the mother is scanty, inconsistent or missing.

One area where meta-analysis of epidemiological data may be particularly useful is collating the published data concerning the teratogenicity of pharmacological or environmental agents ingested or inhaled during pregnancy. When a researcher or clinician must reach an informed opinion concerning the possibility of teratogenic effects of a given therapeutic modality, he often faces contradicting and sometimes controversial results generated by different studies and study methodologies. In these circumstances, decisions concerning teratogenicity traditionally have been based upon a literature review involving a critical, albeit subjective, assessment of the methodology and data presented, possibly influences to some extent by personal experience. The ability of meta-analysis to objectively combine and quantify a potential risk from a number of epidemiological studies would be particularly appealing for the assessment of teratogenic risk.

The tool used to analyze the literature for an overall summary of risk between in utero inhalational exposure to organic solvents and adverse pregnancy outcome is meta-analysis. This meta-analysis will examine two outcomes of interest: major malformations and spontaneous abortion. Major malformation is defined as a malformation which is either potentially life threatening or a major cosmetic defect (577). Spontaneous abortion is defined as the spontaneous termination of pregnancy before 20 weeks gestation based upon the date of the first day of the last normal menses (578). Meta-analysis consists of a *quantitative* component and a *qualitative* component (579, 580, 581). Quantitative meta-analysis deals with the mathematics of aggregating data resulting in the calculation of an overall summary statistic and a confidence interval.

Jenicek (581) defined qualitative meta-analysis as a method of assessing the importance and relevance of medical information coming from several independent sources. This is done via a systematic and uniform application of pre-established criteria of acceptability to original studies. It developed in response to criticism that meta-analysis combines studies with varying degrees of research

quality, that the quantitative result would be uninterpretable without any measure or scrutiny of the methodological quality. Naylor suggests that neglecting quality may cause a "drowning of results" (582). In other words, poorly done studies with invalid results can mask valid results from well done studies. Some researchers advocate investigating quality while others do not. Glass (583) argues that no researcher would advocate poorly designing a study, that one should not ignore existing studies with minor flaws because there are no perfect studies, and that each study does contain some kernel of truth which is of some value. Furthermore, he showed that there often appears to be little if any relationship between the validity of research design and effect size. As a result, researchers using meta-analysis may argue that all studies that meet inclusion criteria requirements set a priori should be included in the meta-analysis.

It should be noted that meta-analysis is not a single method for the aggregation of research results, but a strategy that can employ many different methods. The common characteristic of these methods is the single overall quantitative statistic used to summarize research results on a particular topic.

REVIEW OF METHODS

Meta-Analysis -Is There An Advantage?

Meta-analysis is a relatively new method for reviewing and combining results from multiple clinical trials. Whereas other review methods usually involve narrative discussions of individual trials, a meta-analysis systematically aggregates and quantifies results.

Meta-analysis was described by Sacks et al as a "new discipline that critically reviews and statistically combines the results of previous research" (589). A meta-analysis, therefore, is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated. A further simplification states that meta-analysis is a quantitative summary of research.

The term meta-analysis refers to the practice of using statistical methods to combine the outcomes of a series of different experiments or investigations (583, 575). The terminology arises because a meta-analysis uses a study as the unit of observation and thus the data point for each study is itself a statistical summary based on an analysis of primary data. Meta-analysis is the process of combining study results from many independent studies that can be used to draw conclusions about the effect of a treatment.

This integration of results was largely used in psychology but now has been adopted by a wide range of scientific disciplines including medical sciences. Meta-analysis takes a structured approach to literature review, more so than traditional methods. Traditional methods tend to be generally subjective, lacking informal rules to combining results and may ignore degree of effect and sample size (579).

Meta-analysis is a sound concept with many practical applications. The following comments are not made as an attack on meta-analysis but as a statement about its limitations.

Heterogeneity of studies

Assume that a researcher who plans to conduct a meta-analysis works diligently and locates all clinical trials ever conducted on the research question both published and unpublished. After examination of those trials it is revealed that they are quite heterogenous. Combining their results may be less valid than identifying the one (or two or three) best clinical trials and accepting its (their) data as the answer to the question. The counterargument is that the best trials cannot always be identified and even if one or more are identified as best by one person or group, there will always be others who will not necessarily agree with this assessment. More importantly, the counterargument states lack of agreement about which is best (in other words, highest validity) is the exact reason to do a meta-analysis.

Odds Ratio

Meta-analysis was extensively utilized in the field of education and psychology and was given this meaning of "secondary analysis" by Glass (583). Within meta-analysis there are many ways to combine studies. In general, the basic goal of meta-analysis is to determine or quantify the relationship between one variable and another variable. The magnitude of this relationship is described as effect size.

Classically, meta-analysis addressed how strong the relationship is between two variables. The answer to these questions comes from two parts: the effect size which estimates the magnitude of the relationship and the accuracy of this effect size (584).

The effect size is determined after a thorough literature search is conducted containing the relevant articles meeting the inclusion requirements, Rosenthal's caveat being that these articles must have similar independent variables or in this case organic solvent exposure in the first trimester of pregnancy (584). If independent variables are the same, then the dependent or outcome variable of adverse fetal effects must also be very similar. One type of effect size is calculated by a basic formula which is the difference in mean outcomes of the experimental (exposed, treated) group and control (unexposed, untreated) group, divided by the standard deviation of the outcome in the control group (or by the pooled standard deviation of both groups) (583). The effect size of each meta-analyzed study becomes a new unit of analysis and the heterogeneity of effect sizes can be assessed and an average effect size across studies computed. The statistical advantage to using effect sizes is that there exists a multitude of formulae from which effect size can be derived from, i.e.: chi square, Student's t, P values. Greenland (585) warns that by expressing effects in standard deviation units one can make studies with identical results spuriously appear to yield different results. Also, another problem with using effect size in the 'classical sense' is that effect size can be mathematically converted from heterogeneous or different statistical parameters. Although mathematically correct in the 'classical sense', such a mix of original heterogeneous results is not easy to interpret. Originally conducted in the primary report, statistical analyses were performed to evaluate the confidence in what was observed under the experimental conditions. These analyses are not a measurement of effect by themselves.

Fisher has developed a method to find an overall effect from multiple studies by combining p values. The formula for a summary average value from N number of studies is presented as $\Sigma Zi=-2\ln Pi$ which has a chi-square distribution with 2N degrees of freedom. This method actually reflects the product of individual P values. The overall P value is then obtained by computing the extremeness of this

statistic under the null hypothesis. There are a multitude of ways that summary P value statistics can be obtained. While simple to compute, theses methods are not without their limitations. All of these methods allow combinations of P values for studies which may show effects going in different directions i.e.: a pooled P value does not distinguish between direction of association. In addition, neither the statistic nor the outcome variable has to be identical across studies using these methods. None of these methods addresses the issue of estimation (586). Rosenthal considered the shortcomings of this method (584):

1. can support opposite conclusion, drug A or drug B in different instances can be shown to be a better drug.
2. some methods of combining p-values require small sample size, others require a large sample size.
3. ignores sample size and effect size.
4. may be statistically significant but does not address clinical issue.

In epidemiology, the effect size or the quantitative dimension of the strength and specificity of causal relationships is assessed by a risk measurement. Epidemiological studies are generally of two principal types: cohort (C) and case control (CC). The outcome of a cohort study is the relative risk. For a case control study it is an estimate of the relative risk called the odds ratio (OR). With unbiased sampling and the rare disease assumption, the OR is an approximate measure of the cohort outcome, the relative risk.

The odds ratio is a popular risk measurement used very commonly due to two distinguishing features (587). First, it is the only measure that estimates an interpretable parameter when the data come from a case control study. Second, it has mathematical properties that make it a statistically convenient measure. These features include:

1. solves problems of statistical ambiguity of different denominators. It has an advantage over the risk ratio in that no matter which denominator is chosen, the end result is the same.
2. provided that the case control's population has been properly sampled, then the resulting OR gives a good representation of risk in the population.
3. the OR in suitable circumstances gives an excellent approximation of the risk ratio that would be found in a cohort study of etiology, i.e., in rare disease states.

These features explain why several statistical methods for combining information from 2X2 tables use the odds ratio. The Mantel-Haenszel approach to calculating OR will be used in this study as a quantitative summary statistic (588). L'Abbe (579) has discussed the advantages of using the Mantel-Haenszel method:

1. if the raw data present are categorical, then relatively homogeneous results can be pooled using the Mantel-Haenszel estimation of the combined relative risk.
2. simple, widespread applicability in clinical research.
3. chi square statistic has 1 degree of freedom, hence the significance of the summary measure of exposure and the standard error of the estimate can be used to compute a confidence interval around the relative risk.
4. Mantel-Haenszel estimate of relative risk takes into account the sample size.
5. Mantel-Haenszel method allows the reviewer to incorporate weighting schemes base on quality scores.

Stepwise approach to meta-analysis (579, 575)

1. definition of problem
2. retrieval of studies
3. selection of studies for analysis
4. data extraction
5. quantitative analysis
6. qualitative analysis
7. power analysis
7. conclusions

Step 1. Definition of problem

Before any study can be carried out, it is important to define explicitly the problem of interest. In meta-analysis it is essential that as may studies examining the problem be included in the analysis. Therefore, it is first essential to conduct an extensive literature search for all studies that are available.

Step 2. Retrieval of studies and selection of studies for analysis

Key words include the dependent variable, independent variable and possibly other identifiers that can be used to retrieve information from an on-line database. Once all studies are collected, they can be further selected for analysis according to preset inclusion and exclusion criteria. Sacks recommended that judges be blind and base their decisions on methodology and results (589). Each study was given a code number, methods and results were separated and photocopied. Identifiers such as name of journal, authors, and institution were removed since bias may arise due to prestige/reputation associated with these names may alter the perceived value of results.

Step 3. Inclusion and exclusion criteria

The following should be considered for generalizability of results and hence are questions that should be considered in the inclusion and exclusion criteria.

1. **Range of Patients.**

In order for the conclusions to be valid, and to allow for generalizability of results from a meta-analysis, the patient characteristics should be stated a priori for both cases and controls. Usually, the more narrow the patient scope the more valid the conclusions made at the expense of less generalizability of results. When assessing the teratogenic potential of a given compound using meta-analysis, a number of factors such as age range of patients, primary disease state being treated, severity of disease state, obstetrical history, diet, smoking, alcohol intake, concurrent prescription and non-prescription drug use and socioeconomic status may be important. Because this analysis takes a general approach to the relationship between organic solvent exposure and fetal malformations and spontaneous abortion, data will not be stratified for any of these factors.

2. **Range of Diagnosis.**

It is important to establish a definition of diagnosis in order to allow for combination of results from many studies. The researcher must consider as outcomes: the diagnosis of disease or disorder in groups undergoing treatment as well as diagnosis of adverse reactions (575). In this case, the diagnosis of pregnancy is straightforward. However, the diagnosis of the outcome, a) malformation and b) spontaneous abortion may vary from researcher to researcher and hence results may not be combinable. Therefore, a definition of malformation and spontaneous abortion must have been determined a priori.

3. **Range of Treatment.**

Depending upon the treatment, dosage and length of use may vary from one treatment to another and may play an important role in any adverse effects. Hence, the range of treatments used in the primary studies must be specified, including the dosage and time or length of exposure.

Step 4. Quantitative analysis

Once all the studies have been selected, data must be extracted from the studies into 2X2 tables to prepare data for quantitative analysis.

For a quantitative meta-analysis, the effect size or magnitude of relationship is presented as a summary odds ratio. But before the odds ratio can be calculated, significance tests for the data itself and testing for homogeneity of odds ratio must be determined. Once the odds ratios are tested for homogeneity, either by graphical representations or mathematical equation, the suitable studies will be combined to calculate an overall summary value for the odds ratio and 95% confidence interval. Therefore, meta-analysis provides a objective summary of studies investigating a particular problem.

Naylor points out that although a meta-analysis may yield useful policy guidelines, the quantitative interpretation of the results must be undertaken with caution (582). Differences between studies make it impossible to regard the pooled measures of effect as precise estimates and their confidence intervals cannot be interpreted too strictly. As stated by Peto in an impromptu discussion "the confidence limit is not a confidence limit on what all future trials will be. It's a confidence limit on what was done in these studies, what sort of results would one have expected. It is a confidence limit that is conditional upon what was done" (621).

Step 5. Qualitative analysis

Both critics and meta-analysts agree that a qualitative component in a meta-analysis would be useful (581). However, there is no consensus as to the method of conducting such a qualitative analysis. Jenicek (581) has stated that such a approach represents at present one of the greatest challenges of meta-analysis, that is, to find an ideal method for integration of qualitative and quantitative aspects of meta-analysis in the synthesis of research. Until now the question of what studies to include and how to weight them has not been settled. Several meta-analysts have presented different views on this issue of qualitative meta-analysis (583,590).

One problem facing those performing meta-analyses is the lack of proven method of evaluation of the consistency of information presented in the papers. With more subjective methods of literature review, there is a tendency to place less emphasis on those studies that may have flaws in research methodology (590). Similarly, the objective and structured meta-analytic approach also has been criticized because poorly designed studies are mixed with well designed ones. Critics have argued that using insufficiently valid studies in the analysis may falsely distort results (590). If one detected a serious design flaw that may have influenced the overall results, one could perform a sensitivity analysis. This is done by removing that study from the list and recalculating the summary statistic (OR, summary chi square, and confidence interval). If the results do not change markedly, then the study should remain in the analysis as its inclusion tends to increase the generalizability of results. However, if results differ substantially such as changing from nonsignificant to significant, further analysis is indicated.

An analysis of the relationship between study results and study quality may be revealing. There may be a positive or negative association or none at all. Each of these possibilities has obvious implications for the interpretation of these studies. In the meta-analysis of trials of treatment of mild hypertension, for example, the effect size was largest when the validity of the study design was highest (605).

Similarly, Berlin and Colditz (606) found that the beneficial effect of physical activity in preventing coronary heart disease tended to be larger in methodologically stronger studies than in less well-designed ones. On the other hand, in a meta-analysis of controlled trials of work-site smoking cessation programs the effect was smallest when the methods of study were best, for example if reported smoking habits were verified biochemically (607). Similarly, a review of studies of anticoagulants for acute myocardial infarction reported that "anticoagulant therapy was ranked superior to none more often in reports that failed to fulfill the methodological standards than in those that did" (608). In the meta-analysis of randomized controlled trials of antibiotic prophylaxis in biliary tract surgery, the effect was unrelated to study quality.

Options in the meta-analysis include separate analyses of studies that differ in their quality and a global meta-analysis that takes study quality into account. This may be done by scoring the studies and then weighting them so that better ones carry more weight or by regression analysis or stratification (609). Sensitivity analysis may be especially convincing i.e. repeated analyses, using different decisions about which studies to include or how to weight them.

To avoid the criticism that "in attempting to capture many studies in a quantitative summary, the authors may allow the reader to lose sight of the limitations of the studies on which the meta-analysis is based" (610), explicit attention should always be drawn to these limitations. When a meta-analysis of observational studies of cancer risk in the petrochemical industry was recently criticized on the grounds that the degree of exposure to various substances was not taken into account, the authors were able to respond that the problem was a lack of information in the original studies, as they had pointed out, and was not created by the meta-analysis (611).

REVIEW OF META-ANALYSIS

Meta-analysis is the accumulation of results from many independent studies to help resolve a particular issue. In medical literature the "gold" standard for determining cause and effect whether it be between drug and outcome or intervention and improved health is generally the randomized double blinded control model. It is not infrequent that this model fails to recruit the necessary numbers of patients required for detectable significance. Therefore, meta-analysis becomes useful for aggregating data from small sampled studies for the purpose of addressing a common problem that is found among the aggregate studies. Meta-analysis is not only a statistical method combining numbers. A high amount of expertise is required at each stage of a meta-analysis so that bias in the selection of papers, data and pooling of results can be minimized. Below are listed questions addressing the validity of meta-analysis.

1. How do we avoid selection and data extraction bias?
2. Publication bias, or how do we assure that all the studies obtained for the analysis are really all that is available?
3. Test for homogeneity, are differences in the results pooled together due to random error?

Selection bias

A common criticism of research summaries is that they are not objective or that they are too impressionistic (591). More quantitative efforts by contrast should more objectively synthesize or select the available evidence and the reviewer must decide which of these many studies to include. Several methods have been used to rectify this problem.

The simplest option suggested by Light (591) is to include every available study. When a reviewer has no prior hypothesis, including such diversity may help broaden knowledge. However, the reviewer faces difficulty of trade-offs in this plan

since not all studies are perfect (some have poor study design or some may have obvious numerical errors).

Another option is to establish a set of inclusion and exclusion criteria that is verified by a panel of experts. This method has been used in many meta-analyses and will be the approach used in this study to prevent selection bias.

Data extraction bias can be reduced by having different investigators independently extract data from the published reports. Observers can be blinded by photocopying appropriate sections from each paper and removing all identifying statements and titles. Sacks (589) suggests that judges should be presented a copy of the methodology not the results. The blinded judge must decide whether the studies agree with the inclusion and exclusion criteria already established. This blinding process helps to avoid any bias in decision making based on the prestige, reputation or standards for peer review of the journal in which the study is published and may alter the perceived value of results.

In order to test agreement among judges measures for reliability should be calculated. Cohen has presented a kappa statistic which is useful for determining agreement between two judges for data presented in epidemiologic studies of categorical type and nominal level (592). Cohen's kappa (k) is a value that represents the proportion that chance expected disagreements between two judges do not occur. Use of Cohen's kappa can be considered if categories are exclusive and exhaustive and if both judges work independently of each other. A minimum acceptable kappa value should be agreed upon a priori (575). This is a matter of judgment, with 0.8 being an arbitrary standard that many consider desirable (575). When there is disagreement on either inclusion of papers or data extraction, observers must arrive at a satisfactory solution without compromising the analysis.

Publication Bias

Before incorporation of studies into a meta-analysis, an exhaustive literature search must be carried out to ensure that every study concerning organic solvents as reproductive toxins be considered. Publications (593) provide a few key references on search procedures using computer methods and other techniques.

With regard to the question "when is a dataset complete?", Carr-Hill (619) noted that meta-analysis offers no convincing criterion for delimiting the size of the dataset. He likens the collector of such data to "a squirrel with a vacuum cleaner". For a serious meta-analyst, collecting the data (in other words, finding the relevant studies and filling the gaps) may be the most tedious and time-consuming part of a meta-analysis. In Yusuf's experience it can take three to four years (620).

In many fields of research some studies are less likely to be published than others. One reason could be that results may fail to reject the null hypothesis or are not statistically significant. Also, if results obtained are not coherent with current or prevailing paradigms or existing knowledge, the paper will likely not be published. Hence, if a review includes only published studies, one might argue or suspect that there is a bias to include large or statistically significant results in the meta-analysis.

Researchers in psychology and education have investigated this problem and have found empirical evidence for this opinion. Smith (594) gathered groups of studies assessing 10 innovations in education. She found empirically that average effect sizes were noticeably smaller for unpublished studies than for published studies. Greenwald (584) surveyed authors for their opinions on whether or not they would submit results for publication immediately before more data collection if their initial full-scale test of the focal hypothesis were: a) allow rejection of null hypothesis, mean response for authors was 58%; and b) would not allow rejection of null hypothesis, mean response was 6%. Light argues if these results are even roughly in the realm of reality, we see that a statistically significant finding is nearly

ten times more likely than a non significant finding to be submitted for publication in a refereed journal (591).

Rosenthal has appropriately termed this a "file drawer" problem (584). Rosenthal's view of this problem is the fact that journals are filled with 5% of studies that show Type 1 (alpha) errors whereas the file drawers are filled with 95% of studies that show a non-significant result. Rosenthal has a formula that estimates the number of unpublished trials showing no difference between treatments that would be required to convert a statistically significant pooled difference into a non-significant difference. If this number is small relative to the number of published studies pooled in the meta-analysis then one should be concerned about potential publication bias. A primary disadvantage to this method is that the size of unpublished studies (the number of patients in each treatment group) is not specified. This method is also not clinically significant.

Begg and Pilote (595) have provided another method for estimating potential publication bias that requires estimation of the size of the source population from which the published patient groups are drawn. Using this information and the sample size, maximum potential publication bias can be calculated for an individual study, and Begg provides a table to facilitate calculations. The limitation of Begg's method is that it requires knowledge of the incidence of disease in a specified population and knowledge of the proportion eligible for participation.

L'Abbe et al (579) investigated this problem by developing a method of identifying possible publication bias that simulates single negative randomized trials and varies the size of the treatment groups to raise the probability value above 0.05 (to obtain statistically non-significant difference) when the trial is pooled into the meta-analysis.

Orwin (596) presented a power analysis that will be used in this study. Orwin's formula involves the patient as a study, and effect size is used which has

more clinical significance and will be used in this meta-analysis to determine publication bias. It is straight forward and does not require a computer package.

Homogeneity

When a number of studies are performed to test the same hypothesis there exists a possibility of producing seemingly different findings due to random error or possibly due to difference in research design (systematic error). Since meta-analysis involves the accumulation of findings from various studies it would be prudent to ensure that these results come from a common population and therefore share a common effect. A chi square test for homogeneity examines the hypothesis that all eligible reports are derived from the same population and that the variability among the results was due to random error. However, if a result or set of results occurred due to some flaw in research design or systematic error, the individual studies must be identified and investigated to determine whether they can be included in the meta-analysis (575).

Combined results from different studies with different protocols and populations may yield greater statistical power and statistics in meta-analysis are used to help summarize these results quantitatively. An underlying assumption in combining individual study results to arrive at a summary measure is that their differences are due to chance alone, and therefore all study results are homogenous or reflect the "true effect". If homogeneity does not exist, it may indicate that the pooling of results is not possible due to possible cumulating of some studies with systematic error.

Homogeneity has been examined by many authors:

1. Glass (583) asserted that differences occur in studies due to random error. If independent variables are the same, then random error would cancel out and that meta-analysis would converge on the truth.

2. Sacks (589) and L'Abbe (579) would argue that tests should be done to detect systematic bias. If bias in fact does exist, then the rejected study should be examined individually. Two methods are used to test for homogeneity:

Method I: The Mathematical Approach

Breslow and Day (597) use the logit approach to test for homogeneity which is suitable for any set of risk estimates, including the Mantel-Haenszel odds ratio (OR). This is a chi square test that has k-1 degrees of freedom where k is the number of studies under consideration. Odds ratios are the individual odds ratios calculated in each study and w_i are the weights representing the reciprocal of the variance for the natural logarithm of the OR estimate.

Both the OR and w are calculated after being tested for homogeneity. Breslow and Day warn that this test is subject to instability when N is small and do not recommend it for general practice such as testing homogeneity between strata within a single study. The majority of epidemiological papers consist of large sample sizes hence this is not a serious problem when testing homogeneity of effect between studies.

Other calculations used to test for homogeneity have been presented by DerSimonian and Laird (598). Their report assessed the approach used to incorporate the heterogeneity of effects in the analysis of the overall treatment efficacy. Q statistics, similar to the equation presented by Breslow and Day were used to determine the 'constancy' of treatment effect. The results emphasized that the variation in the treatment effect across several trials is often not negligible and should be incorporated into the analysis of the overall treatment efficacy. The unweighted statistic which assigns an equal weight to each study may not be appropriate for testing homogeneity when differences in sample sizes and/or underlying proportions across studies are large. Therefore, a weighted scheme very similar to Breslow and Day's should be used in testing for combinability of results.

Method II: The Graphical Method

Calculation of chi square as suggested by Breslow and Day may determine if there exists an heterogeneity but it cannot indicate which study is the different study. L'Abbe (579) has suggested to use graphical plots to check for homogeneity. These authors caution against relying on statistical tests alone and argue that the power of statistical tests for homogeneity is often low because most meta-analyses pool the results of a very limited number of individual studies. Investigators should resort to informed subjective judgment and examine a graphic display of study outcomes for homogeneity assumption.

Graphic display of results can be performed as outlined by L'Abbe (579). In the simplest scenario, the outcome consists of only two categories in this study malformation/spontaneous abortion and normal outcome. For notation, use Pc as the proportion of malformed infants in the control group and Pt as the proportion of malformed infants in the experimental group.

If there is a scatter of results, then the outliers should be examined for similarities among each other, possibly a certain group of studies (case control, certain authors, research design) could have caused the results to be different and hence should be analyzed separately. If there is no pattern among the outliers then differences may be attributed to random error and hence all studies can be included in the overall pooled effect.

Reliability

Chalmers and his colleagues assessed the reliability of meta-analysis (599). They reviewed 91 published and unpublished meta-analyses of which 46 papers included replicate analyses of 20 different treatments. Chalmers assessed the level of statistical and clinical agreement between meta-analyses for the same intervention. Overall, they found that of the 20 topics, 10 cohorts agreed statistically and 10 cohorts

disagreed. However, as the authors point out, differences were almost always of degree rather than direction. There were few factors which predicted disagreement between different studies, although statistical methods seemed important in that 8 of 15 meta-analyses that used crude pooling of data disagreed. In comparison, only 6 of 34 meta-analyses that used more sophisticated analytical methods disagreed.

Chalmers' study of reliability was further examined by Henry and Wilson (600) for meta-analyses available since 1987. Overall, the cohort of replicated meta-analyses published since 1987 seem to exhibit greater level of agreement than the studies published before that date. Authors cite this probably due to the general improvement in the quality of studies over time, however, this was not assessed in their paper.

When the disagreeing cohorts were examined more closely, the authors (600) noted clear explanations why each case was different from the other which had more to do with basic problem formulation or differences in the ways in which data were extracted and interpreted than with any fundamental problem with the method of meta-analysis.

METHODS

PROBLEM: Although there may exist independent studies examining the effects of organic solvent exposure in utero and adverse fetal outcomes, there is no overall quantification of risk across all these studies.

DEPENDENT VARIABLE: Malformations, major as defined by Heinonen (577). Spontaneous abortions as defined by Cunningham et al (578).

INDEPENDENT VARIABLE: Organic solvents.

ASSEMBLY OF STUDIES

A literature search was conducted to collect studies for the meta-analysis. Using Medline, Toxline and Dissertation Abstract databases, literature was extracted concerning the problem in question. For this meta-analysis, Medline, Toxline and Dissertation Abstract databases were explored for all research studies of interest. In addition, external colleagues were consulted (regarding unpublished studies) whose area of interest is in occupational exposure and reproductive toxicology. These include: Didi Bentur (Drugs and Chemicals in Pregnancy Program, Israel), Helena Taskinen (Institute of Occupational Health, Finland), Marja-Lisa Lindbohm (Institute of Occupational Health, Finland), Brenda Eskenazi (California Birth Defects Monitoring Program), Gary Shaw (California Birth Defects Monitoring Program), Maureen Paul (University of Massachussetts Medical Center), Gerald Chernoff (Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazards), Shanna Swan (Semiconductor Industry Association - University of California at Davis).

All references from the extracted papers and case reports were investigated. Standard textbooks containing summaries of teratogenicity data were consulted for further undetected references.

Key words employed:

pregnancy, organic solvent, chemical, occupational exposure, adverse fetal outcome, malformation, congenital abnormalities, birth defect, teratogen, abortion, spontaneous abortion

QUANTITATIVE ANALYSIS

Data selection

Articles found in the literature review were obtained as suggested by Sacks (589). The methods section from each article was cut out and identifying markers of the study such as author name, institution, journal title and year were removed to prevent any bias due to prestige in selecting articles for analysis. The articles were cut and stapled to a data collection sheet and presented to two reviewers - Ernest Kopecky and Merry Liau-Chu for selection into analysis.

Reviewers were given a package that included the following:

1. Inclusion/exclusion checklist (Appendix A).
2. The outcomes of interest (malformations) (Appendix B).

Any discrepancies were settled in conference with the two reviewers. To determine inter-rater reliability, the test statistic kappa (κ) was calculated for the judges' assessment of both the methods and results section of each paper. The Pearson correlation coefficient (r) was used for inter-rater reliability of the quality analysis.

Data extraction

Data from the study were extracted with respect to exposure to organic solvents and outcome of major malformations and spontaneous abortion.

Analysis (equations in Appendix F)

1. Calculation of significance of 2X2 tables.
2. Calculation for homogeneity.
3. Calculation of pooled odds ratio.
4. Calculation of significance of summary odds ratio (95% confidence interval - Miettinen method) (601).
5. Orwin's Power calculation.

QUALITATIVE ANALYSIS

To assess the quality of each published study, a questionnaire was utilized that was previously developed for examining both case-control and cohort studies in a meta-analysis (623) (Appendix E). An overall quality index was computed by adding item scores from the questionnaire and dividing by the maximum total possible score; the overall score ranged from 0 to 1. It was decided that the quality scores would be incorporated as analytical weights only if the coefficient of determination between the quality scores and the risk estimates (relative risk or odds ratio) was greater than 20 percent (622). This compromise was based on the fact that some authors believe that the validity of the studies is usually not related to their results and that there is no relation between treatment difference and overall quality score (624).

RESULTS

The literature search yielded 559 articles (1-559). Of these, 549 in total were rejected for the reasons listed in Tables 1-5. The types of papers rejected were: animal studies (298), case reports/series (28), review articles (58), editorials (13), duplicate articles (10), not relevant (62), malformation not specified (29), spontaneous abortion not defined (31), unable to extract data (4), no indication of timing of exposure (16). Five papers were included into the major malformation analysis (Table 6) and 5 papers were included into the spontaneous abortion analysis (Table 7).

Of the papers presented to the raters for inclusion into the analysis the interobserver agreement was as follows:

1. *Malformation analysis:*

   methodology before discussion κ=0.92 95% CI (0.78-0.99)

   methodology after discussion κ=1.00

   results before discussion κ=0.83 95% CI (0.42-1.18)

2. *Spontaneous abortion analysis:*

   methodology before discussion κ=0.71 95% CI (0.44-0.99)

   methodology after discussion κ=1.00

   results before discussion κ=1.00

3. *Malformation quality analysis:*

   r=0.09 (p=0.98)

4. *Spontaneous abortion quality analysis:*

   r=0.69 (p=0.19)

SOURCE OF SUPPORT

The source of funding may have a bearing on the outcome due to bias in selection or evaluation. As a result, the reader may place a greater or lesser credence on the outcome of a study depending on its financing.

Malformations:

In the present meta-analysis, 3 of the studies were supported by government grants or contracts, 1 study was from a research unit (support not stated), and 1 study was a PhD dissertation (support not stated) (Table 8). There was no apparent relationship between the source of funding and findings of the 3 studies in this analysis that reported source of funding.

Spontaneous Abortion:

Two of the studies were reports from research units (support not stated), 1 study was a PhD dissertation (support not stated), 1 study was supported by a charitable organization and 1 study was supported by a private organization. There was no apparent relationship between the source of funding and findings of the 3 studies in this analysis that reported source of funding.

QUALITATIVE RESULTS

For both the malformation and spontaneous abortion sections of the meta-analysis, quality score did not correlate with ORi (Table 17) (Figure 3 and Figure 4). As it was decided a priori that the quality scores would be incorporated as analytical weights only if the coefficient of determination between the quality scores and the risk estimates (relative risk or odds ratio) was greater than 20 percent (622), quality scores were not incorporated as analytical weights.

QUANTITATIVE RESULTS

MALFORMATIONS

In total 5 papers describing results from organic solvent exposure were identified. The summary odds ratio obtained was 1.64 (95% CI: 1.16 - 2.30). The test for homogeneity yielded a chi square of 2.98 (df=4, p=0.561). A graphical method for display of data was used to detect obvious heterogeneity as suggested by L'Abbe (579) (Figure 1). There did not appear to be any obvious outliers. This suggests that heterogeneity observed is not due to systematic bias but to random error.

When studies were analyzed separately according to study type, the chi square value from Breslow and Day's test for homogeneity of effect for cohort studies was 0.52 (df=1, p=0.471) and for case control studies it was 0.01 (df=2, p=0.995). Meta-analysis of both the cohort studies and case-control studies produced similar results. The summary odds ratio for cohort studies was 4.74 (95% CI: 2.08 - 10.81) and 1.62 (95% CI: 1.12 - 2.35) for case-control studies. Estimates of risk for both studies appear to suggest an increase in risk with organic solvent exposure.

The file drawer issue can be examined by using Orwin's formula (similar to power analysis). The power analysis as suggested by Orwin yielded an average effect size for 5 studies: Cohen's d=0.071, the value of d for cohort studies was 0.064 and for case control studies was 0.076 (Table 16). All three are low in absolute value and are considered small according to Cohen's criterion. According to Orwin's formula, decreasing the overall effect size to 0.05 (small effect) would require the addition of 2 studies with an effect size d=0.001 (small effect size).

SPONTANEOUS ABORTION

In total, 5 papers describing results from organic solvent exposure were identified. The summary odds ratio obtained was 1.25 (95% CI: 0.99 - 1.58). The test for homogeneity yielded a chi square=4.88 (df=4, p=0.300). A graphical method for display of data was used to detect obvious heterogeneity as suggested by L'Abbe (579) (Figure 2). There did not appear to be any obvious outliers.

When studies were analyzed separately according to study type, the chi square value from Breslow and Day's test for homogeneity of effect for cohort studies was 4.20 (df=3, p=0.241). Meta-analysis of both cohort and case-control studies produced similar results. The summary odds ratio for cohort studies was 1.39 (95% CI: 0.95 - 2.04) and 1.17 (95% CI: 0.87 - 1.58) for case control studies.

The power analysis as suggested by Orwin yielded an average effect size for 5 studies: Cohen's d=0.095; the value of d for cohort studies was 0.10 and for case control studies was 0.06. All three are low in absolute value and are considered small according to Cohen's criterion. According to Orwin's formula, increasing the overall effect size d to 0.2 (a small effect) would require the addition of 2 studies with an effect size d=0.5 (medium effect size).

SUMMARY OF RESULTS - Malformations

Parameter	Overall studies	Case-control	Cohort
N	7036	5141	1895
n	5	3	2
df	4	2	1
homogeneity χ^2	2.98	0.01	0.52
p	0.561	0.995	0.471
OR summary	1.64	1.62	4.74
95% CI upper	2.30	2.35	10.81
95% CI lower	1.16	1.12	2.08

SUMMARY OF RESULTS - Spontaneous abortions

Parameter	Overall studies	Case-control	Cohort
N	2899	1096	1803
n	5	1	4
df	4	0	3
homogeneity χ^2	4.88		4.20
p	0.300		0.241
OR summary	1.25	1.17	1.39
95% CI upper	1.58	1.58	2.04
95% CI lower	0.99	0.87	0.95

Table 1: List of Papers Rejected for Meta-Analysis of Organic Solvents - Malformations *Methodology*

Ref	Authors	Reason for Rejection
184.	Hemminki et al	major malformation not specified
336.	Olsen et al	no malformations
332.	Ahlborg	no indication of timing of exposure
333.	Erickson et al	no solvent exposure
373.	Ananijevic-Pandey et al	no indication of timing of exposure
207.	Taskinen et al	major malformation not specified
377.	Kallen et al	solvent exposure not specified
220.	McDonald et al	solvent exposure not specified
71.	McDonald et al	solvent exposure not specified
283.	Hemminki et al	abstract
61.	Deane et al	no indication of timing of exposure
15.	Axelsson et al	major malformation not specified
215.	Axelson et al	major malformation not specified
218.	Herz-Picciotto et al	major malformation not specified
230.	Fenster L et al	major malformation not specified
250.	Figa-Talamanca	major malformation not specified
237.	Olsen	no indication of timing of exposure/no normal control
228.	Wrensch et al	major malformation not specified
356.	McDonald et al	no nonexposed control numbers
2.	Ahlborg	major malformation not specified
1.	Tikkanen et al	repeat of data in paper # 21
4.	Taskinen	review article
5.	Lindbohm et al	no malformations
3.	Savitz et al	no malformations
6.	Kurppa et al	repeat of data in paper # 21
8.	Strandberg et al.	letter to the editor
10.	Wrensch et al	major malformation not specified
11.	Windham et al.	major malformation not specified
14.	Holmberg et al	repeat of data in paper # 21
16.	Holmberg et al	repeat of data in paper # 21
17.	Hansson et al	no indication of timing of exposure
18.	Blomqvist et al	no control group
19.	Meirik et al	letter to the editor/no indication of timing of exposure
20.	Lindbohm et al	major malformation not specified
23.	Hunter et al	case report
24.	Hersh et al	case report
25.	Florack et al	review
26.	Eskenazi et al	IQ as outcome
27.	Kucera	case series
29.	Hemminki et al	major malformation not specified

30.	Ng et al	no malformation
31.	Zhang et al	major malformation not specified
33.	Anonymous	no malformations
34.	Fabro	review
35.	Goulet et al	no malformations
36.	Tabacova	review
37.	Schreiner	review
38.	Funes-Cravioto et al	chromosomal aberration (no syndrome)
39.	Hersh	case report
40.	Toutant	case report
41.	Goodwin	case series
42.	Giacoia	review
44.	Lindbohm et al	review
45.	Bolt et al	case report
46.	Conner et al	review/letter
47.	McDonald et al	no malformation
48	Tikkanen et al	repeat of data in paper # 12
49.	Kyyronen et al	major malformation not specified
50.	Pastides et al	major malformation not specified/no indication of timimg of exposure
51.	Nordstrom et al	no control
52.	Nordstrom et al	no solvent exposure
53.	Ng et al	no malformations/no indication of timing of exposure
54.	Heidam	no malformation
55.	Axelsson et al	major malformation not specified
56.	McDiarmid et al	review
57.	Harkonen et al	no indication of timing of exposure
59.	Ericson et al	no indication of timing of exposure
60.	Ericson et al	no indication of timing of exposure
63.	McDonald et al	no malformations
64.	Taskinen et al	no malformations
65.	Theriault et al	no solvent exposure
66.	Heidam	major malformation not specified/no indication of timing of exposure
67.	Hemminki et al	major malformation not specified
68.	Lindbohm et al	major malformation not specified/no indication of timing of exposure
69.	Hemminki et al	no solvent exposure
70.	Edmonds et al	no solvent exposure
71.	McDonald et al	no solvent exposure
72.	McDonald et al	no malfomation
73.	Haas et al	review
74.	Infante et al	no solvent
75.	Edmonds et al	letter to the editor
76.	Goldberg et al	no normal control
77.	Huel et al	no malformation
78.	Baltzar et al	letter to the editor

79.	Mikhailova et al	no malformation
80.	Erickson et al	letter to the editor
81.	Syrovadko	no malformation
82.	Tenenbein	no malformation/abstract
83.	Mukhametova et al	no malformation
84.	Stoltenburg-Didinger et al	animal
151.	Holmberg	case review
185.	Harkonen et al	major malformation not specified/no indication of timing of exposure
190.	Hernberg et al	abstract
191.	Hemminki et al	letter to the editor
197.	Elovaara et al	letter to the editor
214.	Le Leu et al	letter to the editor
216.	Kallen	letter to the editor
217.	Clarke et al	perinatal death
219.	McDonald et al	no solvent exposure
224.	Zierler	editorial
225.	Petitti	editorial
226.	Swan et al	review
227.	Deane et al	major malformation not specified/no indication of timing of exposure
231.	Tikkanen et al	repeat of data in paper # 12
232.	Paustenbach	review
235.	Shaw et al	contaminated drinking water (no inhalational exposure)
236.	Upfal	review
238.	Lindbohm et al	review
239.	Hemminki et al	review
240.	Roeleveld et al	review
241.	Fenston et al	review
246.	Rosenberg et al	review
247.	Hemminki et al	no malformation/no indication of timing of exposure
248.	Hemminki et al	no malformation
249.	Hemminki et al	no malformation
252.	Barroso-Moguel et al	case series
253.	Kestrup et al	no indication of timing of exposure
254.	Dorsch et al	no solvent
255.		abstract
256.	Guiseppina Bosco	major malformation not specified/no indication of timing of exposure
257.	Zierler et al	no solvent
265.	Check	letter /no solvent
267.	Rin et al	case report
268.	Sheikh	letter to the editor
269.	Ahlborg et al	no idication of timing of exposure
270.	Pradat	solvent not specified/no idication of timing of exposure

271.	Fernandez et al	case report
272.	Heidam	no malformation
273.	Savitz et al	major malformation not specified/timing of exposure not specified
274.	Cavedon et al	no malformation
277.	Lindemann	case report
278.	Donald et al	review
280.	Tikkanen et al	repeat of data in paper # 12
281.	Pearson et al	case series
282.	Arnold et al	case report
284.	Seshia et al	case series
285.	Arnold	case series
316.	Huang	no malformation
317.	Kucera	case series
318.	anonymous	no solvent/short report
319.	Steele	major malformation not specified
320.	Brieger et al	review
325.	Taskinen et al	major malformation not specified
335.	van der Gulden	review
344.	Tabacova et al	no malformation/maternal complications
345.	Saxen	no solvent exposure
347.	Silberg et al	major malformation not specified
348.	Lindbohm	no malformation
349.	Streicher et al	case review
350.	Ericson et al	no solvent
355.	Greenberg et al	review
357	Axelsson et al	repeat of data in paper # 9
358.	Schaumburg et al	no malformation
359.	Bordarier et al	case report
342.	McDonald et al	no malformation
85.	Aliverti et al	animal
86.	Anderson et al	animal
87.	Andrew et al	animal
88.	Becci et al	animal
89.	Beliles	animal
90.	Doe et al	animal
91.	Doherty et al	animal
92.	Druckery et al	animal
93.	Gleich	animal
94.	Gofmekler	animal
95.	Green et al	animal
96.	Harris et al	animal
97.	Hemsworth	animal
98.	Hudak et al	animal
99.	Hudak et al	animal
100.	Hudak et al	animal
101.	John et al	animal
102.	John et al	animal

103.	John et al	animal
104.	Kazanina	animal
105.	Keller et al	animal
106.	Knickerbocker	animal
107.	Laborde et al	animal
108.	Lane	animal
109.	Lyng	animal
110.	Marks et al	animal
111.	Minor et al	animal
112.	Murray	animal
113.	Nagano et al	animal
114.	Nawrot et al	animal
115.	Nelson et al	animal
116.	Ruddick et al	animal
117.	Schwetz et al	animal
118.	Schwetz et al	animal
119.	Stula et al	animal
120.	Tabacova	animal
121.	Tabacova	animal
122.	Tabacova	animal
123.	Watanabe et al	animal
124.	Willhite	animal
125.	Wong et al	paternal
126.	Murray et al	animal
127.	Ragucci	review
128.	Gilman	animal
129.	Murray et al	animal
130.	Schwetz et al	animal
131.	Schwetz et al	animal
132.	Thompson et al	animal
133.	Culik et al	animal
134.	Bornschein et al	animal
135.	Hardin et al	animal
136.	Anonymous	animal
137.	Short et al	animal
138.	Short et al	animal
139.	Kimmel et al	animal
140.	Snellings et al	animal
141.	Yakubova et al	animal
142.	Vogin et al	animal
143.	Marks et al	animal
144.	Sheveleva	animal
145.	Shumilina	no malformations
146.	Tuchmann-Duplessis	animal
147.	Von Kreybig	animal
148.	Von Kreybig	animal
149.	Peters et al	animal
150.	John et al	animal

152.	Murray et al	animal
153.	Konhaanpaa et al	animal
154.	Vergiyeva et al	animal
155.	Zlobina	animal
156.	Nelson et al	animal
157.	Nawrot et la	animal
158.	Syrovadko	no malformation
159.	Dorfmueller et al	animal
160.	Bingham et al	animal
161.	John et al	no solvent/animal
162.	Mirkova et al	no solvent/animal
163.	Murray et al	animal
164.	Kratov et al	animal
165.	Ungvary et al	animal
166.	Hardin et al	animal
167.	Tyl et al	animal
168.	Nelson et al	animal
169.	Kato	animal
170.	Miller	animal
171.	Infurma et al	animal
172.	Nelson et al	animal
173.	Rall et al	animal
174.	Infurna et al	animal
175.	Watanabe et al	animal
176.	Matsumoto et al	animal
177.	Hurni et al	animal
178.	Nelson et al	animal
179.	Coate et al	animal
180.	Kelly et al	animal
181.	Kitchin et al	animal
182.	da Silva et al	animal
183.	Lindemann	animal
184.	Hemminki et al	no malformations
185.	Harkonen	no indication of timing of exposure
186.	Mur et al	no solvent
187.	Hemminki et al	review
188.	George et al	animal
189.	Andrew et al	animal
192.	Hebert et al	case report
193.	Kawasaki et al	animal
194.	York et al	animal
195.	Loeber et al	animal
196.	Healy	animal
197.	Elovaara et al	animal
198.	Bross et al	animal
199.	Smith et al	animal
200.	John et al	animal
201.	Bergman	animal

202.	Kankaapaa et al	animal
203.	Levchuck	no malformation
204.	Mirkova	animal
205.	Nelson et al	animal
206.	Ragulye	animal
208.	Baltzar et al	no solvent/no indication of timing of exposure
209.	Minor et al	animal
210.	Overman	animal
211.	Sallenfait et al	animal
212.	Sallenfait etal	animal
213.	Shusterman et al	no malformations
221.	Niemela et al	no solvent
222.	Murray et al	animal
223.	Rogers et al	animal
228.	Wrensch et al	major malformation not specified
233.	Schenker et al	no malformation
234.	Dresser et al	animal
238.	Lindbohm et al	review
239.	Hemminki et al	review
240.	Roeleveld et al	review
241.	Fenston et al	animal
242.	Krasavage et al	animal
243.	Schwetz et al	animal
244.	Nelson et al	animal
245.	Litvinov et al	review
246.	Rosenberg et al	review
251.	Golub et al	review
252.	Barroso-Moguel et al	case series
254.	Dorsch et al	no solvent
261.	McKee et al	animal
263.	Anonymous	review
264.	NIOSH	review
266.	Hall	case report
275.	Hemminki et al	review
276.	Loscalzo et al	case report
281.	Pearson et al	case report
282.	Arnold et al	case report
284.	Seshia et al	case series
285.	Arnold	case series
287.	Press et al	no maternal exposure
288.	Press et al	no maternal exposure
289.	Pradat	no solvent
290.	Euler	animal
291.	Kurzel et al	animal
292.	Ericson et al	no solvent
293.	Saurel-Cubizolles et al	letter
294.	Ericson et al	letter
295.	Axelsson	no solvent exposure

296.	Pradat	no solvent exposure
297.	Nordstrom et al	no solvent exposure
298.	Hemminki et al	no solvent exposure
299.	Hemminki et al	no solvent exposure
300.	Holmberg et al	no solvent exposure
301.	Hardin et al	animal
302.	Brown etal	animal
303.	Andrew et al	animal
304.	Anonymous	letter
305.	Heseltine etal	no maternal exposure
306.	Soden	no maternal exposure
307.	Martin	animal
308.	Yonemoto et al	animal
309.	Wilkins-Hang et al	review
310.	Nelson etal	animal
322.	Kolmodin-Hedman et al	no malformations
323.	Yakibova etal	no malformations
324.	Pinney	no malformations
326.	Schottek	animal
327.	Saxen	no solvent exposure
328.	Fenster	no malformation
329.	Neurtra et al	review
330.	Hertz-Picciotto etal	review
331.	Wrensch et al	review
334.	Taskinen	review
336.	Olsen et al	review
338.	Tikkanen et al	repeat of data in paper # 12
339.	Hemminki et al	no solvent
340.	Eskenazi etal	review
341.	Miller	review
343.	Selevan et al	no solvent
344.	Tavacova et al	no malformation
345.	Saxen	no solvent
346.	Lindbohm et al	no solvent
347.	Silberg etal	major malformation not specified
349.	Streicher etal	case series
350.	Ericson etal	no solvent
351.	Persaud	review
354.	McDonald eta l	editorial
357.	Axelsson et al	no solvent
360.	Lindbohm	review
361.	Lindbohm	review
364.	Gates	review
365.	Paul et al	review
366.	Clarke et al	no solvent
367.	Anonymous	review
368.	Di Carlo et al	review
373.	Ananijevic-Pandey et al	no solvent

374.	Mattison	review
375.	Laham et al	no malformation
376.	Monster et al	no malformation
377.	Kallen et al	timing of exposure not specified
378.	Anonymous	review
379.	Hevelin	review
380.	Hemminki et al	review
381.	Chernoff et al	abstract
382.	Ali et al	review
383.	Campbell et al	animal
384.	O'Shea et al	animal
385.	Popov et al	animal
386.	Skosyrova	animal
387.	Veghelyi eta l	review
388.	Webster etal	animal
389.	Kennedy	animal
390.	Thiersch	animal
391.	von Kreybig	animal
392.	von Kreybig et al	animal
393.	Wright	animal
394.	Oser et al	animal
395.	Johannsen et al	animal
396.	Smith et al	animal
397.	Smith et al	animal
398.	Wilhite	animal
399.	Field et al	animal
401.	Sugiyama etal	animal
402.	Kolesnichenko et al	animal
403.	Price et al	animal
404.	Kitaev et al	animal
405.	Pushkina et al	animal
406.	Watanabe et al	animal
407.	Vesselinovitch et al	animal
408.	Duraiswami	animal
409.	Wicramaratue etal	animal
410.	Ruddick et al	animal
411.	Carpenter et al	animal
412.	Hackett et al	animal
413.	Morrissey et al	animal
414.	Brightwell et al	animal/abstract
415.	Denise et al	animal
416.	Nelson et al	animal
417.	Bus et al	animal
418.	Sleet et al	animal
419.	Hardin et al	animal
420.	Kimmel et al	animal
421.	Tabacova eta l	animal
422.	Adams et al	animal

423.	Roschlau et al	animal
424.	Tsirelnikov eta l	animal
425.	Wilson	animal
426.	Black et al	animal
427.	Litchfield et al	animal
428.	Coate et al	animal
430.	Picciano et al	animal
431.	Kurosaki et al	animal
432.	Smith etal	animal
433.	Giavini et al	animal
434.	Hayes et al	animal
435.	Kennedy etal	animal
436.	Alumot et al	animal
437.	Tyl et al	animal
438.	Cook et al	animal
439.	Ema et al	animal
440.	Hardin	animal
441.	Hardin et al	animal
442.	Nagano et al	animal
443.	Nelson et al	animal
444.	Nolan et al	animal
445.	Stenger et al	animal
446.	Wichramaratne	animal
447.	Krasavage et al	animal
448.	Generoso et al	animal
449.	Thiersch	animal
450.	Johannsen et al	animal
451.	Guest et al	animal
452.	Hellwig et al	animal
453.	Plasterer et al	animal
454.	Price et al	animal
455.	Wolkowski-Tyl et al	animal
456.	Ungvary et al	animal
457.	Haar et al	review
458.	Bariljak et al	animal
459.	Lamb etal	animal
460.	Laborde et al	animal
461.	Antledge et al	animal
462.	Smith	animal
463.	Snellings et al	animal
464.	Nelson et al	animal
465.	Saito et al	animal
466.	Ma etal	review
467.	Overman	animal
468.	Kennedy	animal
469.	Rao et al	animal
470.	Vozovaya	animal
471.	Vozovaya	animal

472.	Dawson et al	animal
473.	Alumot et al	animal
474.	Anderson et al	animal
475.	Murray et al	animal
476.	Short et al	animal
477.	Hanley et al	animal
478.	Kawasaki et al	animal
479.	Hardin et al	animal
480.	Price et al	animal
481.	Ferenz et al	animal
482.	Solomon et al	animal
483.	Andrews et al	animal
484.	Courtney et al	animal
485.	Khera et al	animal
486.	Miller et al	animal
487.	Khera etal	animal
488.	Das et al	animal
489.	Johns et al	animal
490.	Brittelli et al	animal
491.	Chaube et al	animal
492.	Andrews et al	animal/abstract
493.	Youssef et al	animal/abstract
494.	Merkle et al	animal
495.	Conaway et al	animal
496.	Feuston etal	animal
497.	Nelson et al	animal/abstract
498.	Scott et al	animal
499.	Sleet etal	animal
500.	Sleet etal	animal
501.	Wilsch etal	animal
502.	Wolkowski-Tyl etal	animal
503.	Schwetz et al	animal
504.	Pfeifer etal	animal
505.	Tyl et al	animal
506.	Vander Hoeve et al	animal
507.	Anonymous	review
508.	Dodd et al	animal
509.	Tyl et al	animal
510.	Serrone et al	animal
511.	Ruddick et al	animal/review
512.	Gray et al	animal
513.	Scortichini et al	animal
514.	Slott et al	animal
515.	Courtney et al	animal
516.	Hood et al	animal/review
517.	Olsen et al	letter to the editor
518.	Pradhan et al	review
519.	Zielhuis et al	review

520.	Sikov	animal
521.	Kacew et al	animal
522.	Hassoren et al	animal
523.	Sonawane et al	animal
524.	Hudak et al	animal
525.	Nawrot et al	animal/abstract
526.	Dawson et al	animal
527.	George et al	animal
528.	Guest et al	animal
529.	Hall	animal
530.	Ferm	animal
531.	Itoh et al	animal
532.	Luebke et al	animal
533.	Nishimura et al	animal
534.	Sinclair	animal
535.	Takaori et al	animal
536.	Anonymous	animal
537.	Rosen et al	animal
538.	Shigeta et al	animal
539.	Ungvary et al	animal
540.	Gyo et al	animal
541.	Garcia-Estrada et al	animal
542.	Kristensen et al	paternal
543.	Scala et al	animal
544.	Hashizume et al	animal
545.	Geschwind et al	no solvent exposure
546.	Gyo et al	no solvent/non maternal
547.	Vineis et al	animal
548.	Brender et al	paternal
549.	James et al	animal
550.	Hoglund et al	paternal
551.	Oudiz et al	animal
552.	Sohnlein et al	animal
553.	Rayburn et al	animal
554.	Rayburn et al	animal
555.	Zielhius et al	review
556.	Wess et al	review
557.	Cordier et al	review
558.	Cheever et al	animal
559.	Dugard et al	no maternal exposure
260.	Cai et al	no malformation
286.	Lemasters et al	no malformation
352.	Katz et al	no malformation
400.	Schialli et al	review
429.	Bililes et al	animals
279.	Lemasters et al	no malformation
363.	Sikov et al	review
369.	Tatrai et al	animal

370.	Schaufler et al	animal
371.	Gebhardt et al	animal
362.	Brown et al	animal
312.	Ong et al	no maternal exposure
311.	Partanen et al	no maternal exposure
313.	Ulsamer et al	no solvent exposure
314.	Kennedy et al	no solvent exposure
315.	Oakley et al	no solvent exposure
62.	Swan et al	contaminated drinking water (non inhalational)
337.	Tikkanen et al	repeat of study # 12

Table 2: Studies of Teratogenicity of Organic Solvents Meeting the Criteria for Meta-Analysis *Methodology*

Ref	Authors
7.	McDonald et al
9.	Axelsson et al
12.	Tikkanen et al
21.	Holmberg et al
22.	Cordier et al
43.	Ahlborg et al
58.	Lindbohm et al
321.	Lemasters et al
356.	McDonald et al

Table 3: List of Papers Rejected for Meta-Analysis of Organic Solvents - Spontaneous Abortion *Methodology*

Ref	Authors	Reason for Rejection
6.	Kurppa et al	no spontaneous abortion
22.	Cordier et al	no spontaneous abortion
76.	Goldberg et al	no spontaneous abortion
16.	Holmberg et al	no spontaneous abortion
9.	Axelsson et al	spontaneous abortion undefined
184.	Hemminki et al	spontaneous abortion undefined
32.	Halling	no solvent
12.	Tikkanen et al	no spontaneous abortion
231.	Tikkanen et al	no spontaneous abortion
336.	Olsen et al	no spontaneous abortion
332.	Ahlborg et al	no spontaneous abortion
357.	Axelsson et al	no spontaneous abortion
333.	Erickson et al	no spontaneous abortion
373.	Ananijevic-Pandey et al	no spontaneous abortion
207.	Taskinen et al	no spontaneous abortion
377.	Kallen et al	no spontaneous abortion
220.	McDonald et al	spontaneous abortion undefined
71.	McDonald et al	no solvent
283.	Hemminki et al	abstract
215.	Axelson et al	spontaneous abortion not <20 weeks
218.	Herz-Picciotto et al	spontaneous abortion not <20 weeks
250.	Figa-Talamanca	spontaneous abortion undefined
1.	Tikkanen et al	spontaneous abortion not <20 weeks
13.	Holmberg et al	spontaneous abortion not <20 weeks
14.	Holmberg et al	no spontaneous abortion
237.	Olsen et al	no spontaneous abortion
62.	Swan et al	no spontaneous abortion
228.	Wrensch et al	spontaneous abortion not <20 weeks
280.	Tikkanen et al	no spontaneous abortion
337.	Tikkanen e al	no spontaneous abortion
208.	Baltzar et al	no spontaneous abortion
356.	McDonald et al	no spontaneous abortion
338.	Tikkanen et al	no spontaneous abortion
49.	Kyyronen et al	spontaneous abortion undefined
321.	Lemasters	no spontaneous abortion
2.	Ahlborg et al	spontaneous abortion not <20 weeks
3.	Savitz et al	no spontaneous abortion
4.	Taskinen et al	spontaneous abortion undefined
7.	McDonald et al	spontaneous abortion not <20 weeks
8.	Strandberg et al	letter to the editor
10.	Wrensch et al	contaminated drinking water (non inhalational)
15.	Axelsson et al	spontaneous abortion undefined

16.	Holmberg et al	no spontaneous abortion
17.	Hansson et al	spontaneous abortion not <20 weeks
18.	Blomqvist et al	no spontaneous abortion
19.	Meirik et al	spontaneous abortion undefined
20.	Lindbohm et al	spontaneous abortion undefined
21.	Holmberg et al	no spontaneous abortion
22.	Cordier et al	no spontaneous abortion
23.	Hunter et al	case report
24.	Hersh et al	case report
25.	Florack et al	review
26.	Eskenazi et al	IQ
27.	Kucera	no spontaneous abortions/case series
30.	Ng et al	no spontaneous abortion
31.	Zhang et al	spontaneous abortion not <20 weeks
33.	Anonymous	spontaneous abortion undefined
34.	Fabro	review
35.	Goulet et al	no spontaneous abortion
36.	Tabacova	review
37.	Schreiner	review/animal
38.	Funes-Cravioto et al	chromosomal aberration (no syndromes)
39.	Hersh	case report
40.	Toutant et al	case report
41.	Goodwin	case series
42.	Giacoia	review
43.	Ahlborg	no spontaneous abortion
44.	Lindbohm et al	review
45.	Bolt et al	case report
46.	Conner et al	review/letter
48.	Tikkanen et al	no spontaneous abortion
50.	Pastides et al	spontaneous abortion not <20 weeks
51.	Nordstrom et al	no solvent
52.	Nordstrom et al	no solvent exposure
53.	Ng et al	spontaneous abortion not <20 weeks
54.	Heidam	spontaneous abortion undefined
55.	Axelsson et al	spontaneous abortion undefined
56.	McDiarmid et al	review
57.	Harkonen et al	spontaneous abortion undefined
59.	Ericson et al	no spontaneous abortion
60.	Ericson et al	spontaneous abortion not <20 weeks
61.	Deane et al	contaminated drinking water (non inhalational)
63.	McDonald et al	spontaneous abortion undefined
64.	Taskinen et al	spontaneous abortion not <20 weeks
65.	Theriault et al	no solvent
66.	Heidam	spontaneous abortion undefined
67.	Hemminki et al	spontaneous abortion undefined
68.	Lindbohm et al	spontaneous abortion undefined
69.	Hemminki et al	no solvent
70.	Edmonds et al	no solvent

72.	McDonald et al	no spontaneous abortion
73.	Haas et al	review
74.	Infante	no solvent
75.	Edmonds et al	letter to the editor
77.	Huel et al	spontaneous abortion undefined
78.	Baltzar et al	letter to the editor
79.	Mikhailova et al	no spontaneous abortion
82.	Tenenbein	no spontaneous abortion
83.	Mukhametova et al	no spontaneous abortion
84.	Stoltenburg-Didinger et al	animal
151.	Holmberg et al	case series
185.	Harkonen et al	spontaneous abortion undefined
190.	Hernberg et al	abstract
191.	Hemminki et al	letter to the editor
197.	Elovaara et al	letter to the editor
214.	Le Leu et al	letter to the editor
216.	Kallen et al	letter to the editor/no solvent
217.	Clarke et al	perinatal death/no solvent
220.	McDonald et al	no spontaneous abortion
224.	Zierler	editorial
225.	Petitti	editorial
226.	Swan et al	review
227.	Deane et al	contaminated drinking water (non inhalational)
229.	Windham et al	contaminated drinking water (non inhalational)
230.	Fenster et al	contaminated drinking water (non inhalational)
231.	Tikkanen et al	no spontaneous abortion
232.	Paustenbach	review
235.	Shaw et al	no spontaneous abortion
236.	Upfal	review
237.	Olsen	no spontaneous abortion
238.	Lindbohm et al	review
239.	Hemminki et al	review
241.	Fenston et al	animal
246.	Rosenberg et al	review
247.	Hemminki et al	spontaneous abortion not <20 weeks
248.	Hemminki et al	spontaneous abortion undefined
249.	Hemminki et al	spontaneous abortion undefined
250.	Figa-Talamanca	spontaneous abortion undefined
252.	Barroso-Moguel et al	case series
253.	Kestrup etal	spontaneous abortion undefined
254.	Dorsch et al	no solvent
255.		abstract
256.	Guiseppina Bosco et al	spontaneous abortion undefined
257.	Zierler et al	no solvent
265.	Check	letter/no solvent
267.	Rin et al	case report
268.	Sheikh	letter to the editor
269.	Ahlborg et al	spontaneous abortion undefined

270.	Pradat	spontaneous abortion not <20 weeks
271.	Fernandez et al	case report
272.	Heidam	spontaneous abortion undefined
274.	Cavedon et al	spontaneous abortion undefined
277.	Lindemann	case report
278.	Donald et al	review
280.	Tikkanen et al	no spontaneous abortion
281.	Pearson et al	case series
282.	Arnold et al	case report
284.	Seshia et al	case series
285.	Arnold	case series
316.	Huang	spontaneous abortion undefined
317.	Kucera	case series
318.	Anonymous	short report/review
320.	Brieger et al	review
325.	Taskinen et al	review
337.	Tikkanen et al	no spontaneous abortion
338.	Tikkanen et al	no spontaneous abortion
340.	Eskenazi et al	no spontaneous abortion
344.	Tabacova et al	maternal pregnancy complications
345.	Saxen	no solvent
347.	Silberg et al	no spontaneous abortion
348.	Lindbohm	spontaneous abortion undefined
349.	Streicher et al	case review
350.	Ericson et al	no solvent
351.	Persaud	review
355.	Greenberg et al	review
356.	McDonald et al	no spontaneous abortion
357.	Axelsson et al	spontaneous abortion undefined
358.	Schaumburg et al	spontaneous abortion undefined
359.	Bordarier et al	case report
373.	Ananijevic-Pandey et al	no spontaneous abortion
342.	McDonald et al	spontaneous abortion undefined
81.	Syrovadko	no spontaneous abortion
85.	Aliverti et al	animal
86.	Anderson et al	animal
87.	Andrew et al	animal
88.	Becci et al	animal
89.	Beliles	animal
90.	Doe et al	animal
91.	Doherty et al	animal
92.	Druckrey	animal
93.	Gleich	animal
94.	Gofmekler	animal
95.	Green et al	animal
96.	Harris et al	animal
97.	Hemsworth	animal
98.	Hudak et al	animal

99.	Hudak et al	animal
100.	Hudak et al	animal
101.	John et al	animal
102.	John et al	animal
103.	John et al	animal
104.	Kazanina	animal
105.	Keller et al	animal
106.	Knickerbocker	animal
107.	Laborde et al	animal
108.	Lane	animal
109.	Lyng	animal
110.	Marks et al	animal
111.	Minor et al	animal
112.	Murray	animal
113.	Nagano et al	animal
114.	Nawrot et al	animal
115.	Nelson et al	animal
116.	Ruddick et al	animal
117.	Schwetz et al	animal
118.	Schwetz et al	animal
119.	Stula et al	animal
120.	Tabacova	animal
121.	Tavacova et al	animal
122.	Tavacova et al	animal
123.	Watanabe et al	animal
124.	Willhite	animal
125.	Wong et al	paternal
126.	Murray et al	animal
127.	Ragucci	review
128.	Gilman	animal
129.	Murray et al	animal
130.	Schwetz et al	animal
131.	Schwetz et al	animal
132.	Thompson et al	animal
133.	Culik et al	animal
134.	Bornschein et al	animal
135.	Hardin et al	animal
136.	Anonymous	animal
137.	Short et al	animal
138.	Short et al	animal
139.	Kimmel et al	animal
140.	Snellings et al	animal
141.	Yakubova et al	animal
142.	Vogin et al	animal
143.	Marks et al	animal
144.	Sheveleva	animal
145.	Shumilina	no spontaneous abortion
146.	Tuchmann-Duplessis et al	animal

147.	Von Kreybig	animal
148.	Von Kreybig	animal
149.	Peters et al	animal
150.	John et al	animal
152.	Murray et al	animal
153.	Konhaanpaa et al	animal
154.	Vergiyeva et al	animal
155.	Zlobina et al	animal
156.	Nelson et al	animal
157.	Nawrot et al	animal
158.	Syrovadko et al	no spontaneous abortion
159.	Dorfmueller et al	animal
160.	Bingham et al	animal
161.	John et al	animal
162.	Mirkova et al	animal
163.	Murray et al	animal
164.	Kratov et al	animal
165.	Ungvary et al	animal
166.	Hardin et al	animal
167.	Tyl et al	animal
168.	Nelson et al	animal
169.	Kato	animal
170.	Miller	animal
171.	Infurna et al	animal
172.	Nelson et al	animal
173.	Rall etal	animal
174.	Infurna et al	animal
175.	Watanabe et al	animal
176.	Matsumoto et al	animal
177.	Hurni et al	animal
178.	Nelson et al	animal
179.	Coate et al	animal
180.	Kelly et al	animal
181.	Kitchin et al	animal
182.	da Silva et al	animal
183.	Lindemann	case report
186.	Mur et al	no solvent
187.	Hemminki et al	review
188.	George et al	animal
189.	Andrew et al	animal
192.	Hebert et al	review
193.	Kawasaki et al	animal
194.	York et al	animal
195.	Loeber et al	animal
196.	Healy et al	animal
198.	Bross et al	animal
199.	Smith et al	animal
200.	John et al	animal

201.	Bergman	animal
202.	Kankaapaa et al	animal/no maternal exposure
203.	Levchuck	animal
204.	Mirkova et al	animal
205.	Nelson et al	animal
206.	Ragulye	animal
207.	Taskinen	paternal
210.	Overman	animal
211.	Sallenfait et al	animal
212.	Sallenfait et al	animal
221.	Niemela et al	no maternal exposure
222.	Murray et al	animal
223.	Rogers et al	animal
224.	Zierler	editorial
225.	Petitti	editorial
226.	Swan et al	review
234.	Dresser et al	animal
242.	Krasavage et al	animal
243.	Schwetz et al	animal
244.	Nelson et al	animal
245.	Litvinov et al	animal
251.	Golub	review
252.	Barroso-Moguel et al	case series
258.	Druckery et al	animal
259.	Givelber et al	animal
261.	McKee et al	animal
262.	Anonymous	animal/review
263.	Anonymous	review
264.	NIOSH	review
266.	Hall	case series
275.	Hemminki et al	review
276.	Loscalzo et al	case report
281.	Pearson et al	case report
282.	Arnold et al	case report
287.	Press et al	no maternal exposure
288.	Press et al	no materna exposure
289.	Pradat	no spontaneous abortion
290.	Euler	animal
291.	Kurzel et al	review
292.	Ericson et al	no solvent
293.	Saurel-Cubizolles et al	letter
294.	Ericson et al	letter
295.	Axelsson	no solvent
296.	Pradat	no spontaneous abortion
297.	Nordstrom et al	no spontaneous abortion
298.	Hemminki et al	no solvent
299.	Hemminki et al	no spontaneous abortion
300.	Holmberg et al	no spontaneous abortion

301.	Hardin et al	animal
302.	Brown et al	animal
303.	Andrew et al	animal
304.	Anonymous	review
305.	Heseltine et al	review
306.	Soden	no maternal exposure
307.	Martin	animal
308.	Yonemoto et al	animal
309.	Wilkins-Hang et al	review
310.	Nelson	animal
322.	Kolmodin-Hedman	no spontaneous abortion <20 weeks
323.	Yakubova et al	no spontaneous abortion
326.	Schottek	review
327.	Saxen et al	no spontaneous abortion
328.	Fenster et al	review
329.	Neutra et al	review
330.	Hertz-Picciotto et al	review
331.	Wrensch et al	review
334.	McDonald et al	review
339.	Hemminki et al	no spontaneous abortion
341.	Miller	review
342.	McDonald et al	no solvent
343.	Selevan et al	review
346.	Lindbohm et al	review
347.	Silberg et al	no spontaneous abortions
351.	Persaud	review
353.	Axelsson et al	no solvent
354.	McDonald et al	editorial
360.	Lindbohm	review
361.	Lindbohm	review
364.	Gates	review
365.	Paul et al	review
366.	Clarke et al	short article
367.	Anonymous	review
368.	Di Carlo et al	review
372.	Dowty et al	no spontaneous abortion
374.	Mattison	review
375.	Laham et al	no spontaneous abortion
378.	Anonymous	review
379.	Hevelin	review
380.	Hemminki	review
381.	Chernoff	abstract
382.	Ali et al	animal
383.	Campbell et al	animal
384.	O'Shea et al	animal
385.	Popov et al	animal
386.	Skosyrova	animal
387.	Veghelyi et al	animal

388.	Webster et al	animal
389.	Kennedy	animal
390.	Thiersch	animal
391.	von Kreybig et al	animal
392.	von Kreybig et al	animal
393.	Wright	animal
394.	Oser et al	animal
395.	Johannsen et al	animal
396.	Smith et al	animal
397.	Smith et al	animal
398.	Willhite	animal
399.	Field et al	animal
401.	Sugiyama et al	animal
402.	Kolesnichenko et al	animal
403.	Price et al	animal
404.	Kitaev et al	animal
405.	Pushkina et al	animal
406.	Watanabe et al	animal
407.	Vesselinovitch et al	animal
408.	Duraiswami	animal
409.	Wicramaratue et al	animal
410.	Ruddick et al	animal
411.	Carpenter et al	animal
412.	Hackett et al	animal
413.	Morrissey t al	animal
414.	Brightwell et al	animal
415.	Denise et al	animal
416.	Nelson et al	animal
417.	Bus et al	animal
418.	Sleet et al	animal
419.	Hardin et al	animal
420.	Kimmel et al	animal
421.	Tabacova et al	animal
422.	Adams et al	animal
423.	Roschlau et al	animal
424.	Tsirelnikov et al	animal
425.	Wilson	animal
426.	Black et al	animal
427.	Litchfield et al	animal
428.	Coate et al	animal
430.	Picciano et al	animal
431.	Kurosaki et al	animal
432.	Smith et al	animal
433.	Giavini et al	animal
434.	Hayes et al	animal
435.	Kennedy et al	animal
436.	Alumot et al	animal
437.	Tyl et al	animal

438.	Cook	animal
439.	Ema et al	animal
440.	Hardin et al	animal
441.	Hardin et al	animal
442.	Nagano et al	animal/paternal
443.	Nelson et al	animal
444.	Nolan et al	animal
445.	Stenger et al	animal
446.	Wichramaratne	animal
447.	Krasavage et al	animal
448.	Generoso et al	animal
449.	Thiersch	animal
450.	Johannsen et al	animal
451.	Guest et al	animal
452.	Hellwig et al	animal
453.	Plasterer et al	animal
454.	Price et al	animal
455.	Wolkowski-Tyl et al	animal
456.	Ungvary et al	animal
457.	Haar	review
458.	Bariljak et al	animal
459.	Lamb et al	animal
460.	Laborde et al	animal
461.	Antledge et al	animal
462.	Smith et al	review
463.	Snellings et al	animal
464.	Nelson et al	animal
465.	Saito et al	animal
466.	Ma	review
467.	Overman	animal
468.	Kennedy	animal
469.	Rao et al	review/animal
470.	Vozovaya	animal
471.	Vozovaya	animal
472.	Dawson et al	animal
473.	Alumot et al	animal
474.	Anderson et al	animal
475.	Murray et al	animal
476.	Short et al	animal
477.	Hanley et al	animal
478.	Kawasaki et al	animal
479.	Hardin et al	animal
480.	Price et al	animal
481.	Ferenz et al	animal
482.	Solomon et al	animal
483.	Andrews et al	animal
484.	Courtney et al	animal
485.	Khera	animal

486.	Miller et al	animal
487.	Khera et al	animal
488.	Das et al	animal
489.	Johns et al	animal
490.	Brittelli et al	animal
491.	Chaube et al	animal
492.	Andrews et al	animal
493.	Youssef et al	animal
494.	Merkle et al	animal
495.	Conaway et al	animal
496.	Feuston et al	animal
497.	Nelson et al	animal
498.	Scott et al	animal
499.	Sleet et al	animal
500.	Sleet et al	animal
501.	Welsch et al	animal
502.	Wolkowski-Tyl et al	animal
503.	Schwetz et al	animal
504.	Pfeifer et al	animal
507.	Anonymous	review
508.	Dodd et al	animal
509.	Tyl et al	animal
510.	Serrone et al	animal
511.	Ruddick et al	animal/abstract
512.	Gray et al	animal/abstract
513.	Scortichini et al	animal
514.	Slott et al	animal
515.	Courtney et al	animal
516.	Hood et al	review
517.	Olsen et al	no spontaneous abortion/letter
518.	Pradham et al	review
519.	Zielhius et al	review
520.	Sikov et al	animal
521.	Kacew et al	animal
522.	Hassoren et al	animal
523.	Sonawane et al	animal
524.	Hudak et al	animal
525.	Nawrot et al	animal/abstract
526.	Dawson et al	animal
527.	George et al	animal
528.	Guest et al	animal
529.	Hall et al	animal
530.	Ferm	animal
531.	Itoh et al	animal
532.	Luebke et al	animal
533.	Nishimura et al	animal
534.	Sinclair	animal
535.	Takaori et al	animal

536.	Anonymous	animal
537.	Rosen et al	animal
538.	Shigeta et al	animal
539.	Ungvary et al	animal
540.	Gyo et al	no solvent
541.	Garcia-Estrada et al	animal
542.	Kristensen et al	paternal
543.	Scala et al	animal
544.	Hashizume et al	animal
545.	Geschwind et al	no solvent
546.	Gyo et al	no solvent
547.	Vineis et al	no spontaneous abortion
548.	Brender et al	paternal
549.	James et al	animal
550.	Hoglund et al	paternal
551.	Oudiz et al	animal
552.	Sohnlein et al	animal
553.	Rayburn et al	animal
554.	Rayburn et al	animal
555.	Zielhius et al	review
556.	Wess et al	review
557.	Cordier et al	review
558.	Cheever et al	animal
559.	Dugard et al	no spontaneous abortion
260.	Cai et al	no spontaneous abortion
286.	Lemasters et al	no spontaneous abortion
352.	Katz et al	no spontaneous abortion
400.	Schialli	review
429.	Beliles et al	animal
279.	Lemasters	no spontaneous abortion
363.	Sikov et al	animal
369.	Tatrai et al	animal
370.	Scheufler et al	animal
371.	Gebhardt et al	animal
362.	Brown et al	animal
312.	Ong et al	no maternal exposure
311.	Partanen et al	no maternal
313.	Ulsamer et al	no solvent
314.	Kennedy et al	no solvent
315.	Oakley et al	no solvent
319.	Steele	no unexposed data

Table 4: Studies of Spontaneous Abortion of Organic Solvents Meeting Criteria for Meta-Analysis *Methodology*

Ref	Authors
11.	Windham et al
28.	Lipscomb et al
233.	Schenker et al
324.	Pinney
340.	Eskenazi et al

Table 5: Studies of the Teratogenicity of Organic Solvents Rejected from Meta-Analysis *Results*

Ref	Authors	Reason for Rejection
7	McDonald et al	unable to extract crude data for 2X2 tables
43.	Ahlborg et al	unable to extract crude data for 2X2 tables
58.	Lindbohm et al	unable to extract crude data for 2X2 tables
356.	McDonald et al	unable to extract crude data for 2X2 tables

Table 6: Studies of Teratogenicity of Organic Solvents Meeting Criteria for Meta-Analysis

Ref	Authors	Study Type	Data Collection	Malformation Described
9.	Axelsson et al	CC	R	serious malformations (SB & LB)
12.	Tikkanen et al	CC	R* time and area	VSD, CAS, ASD, LHHS (SB & LB)
21.	Holmberg et al	CC	R* time and area	CNS, oral clefts, musculoskeletal, CV defects (SB & LB)
22.	Cordier et al	CC	R* area	major malformations (SB & LB&TA)
321.	Lemasters	C	R	major malformations (LB)

N = 5

* matched control group
CC=Case control
C=Cohort
R=Retrospective

Table 7: Studies of Spontaneous Abortion of Organic Solvents Meeting Criteria for Meta-Analysis

Ref	Authors	Study Type	Data Collection
11.	Windham et al	CC	R
28.	Lipscomb et al	C	R
233.	Shenker et al	C	P* age and ethnicity
324.	Pinney	C	R
340.	Eskenazi et al	C	P* age, race, gravidity, marital status

N=5

* matched control group
CC=Case control
C=Cohort
R=Retrospective
P=Prospective

Table 8: Source of Support - Studies of Teratogenicity in Meta-Analysis

Total Studies = 5

1. Studies supported by government grants or contracts = 3/5

2. Research units/institutes (support not stated) = 1/5

3. Support not stated (PhD Dissertation) = 1/5

Ref	Author	Source of Support
9.	Axelsson et al	Swedish Work Environment Fund
12.	Tikkanen et al	Grant from the Finnish Academy
21.	Holmberg et al	Support not stated: a) Dept Epidemiology and Biostatistics, Institute of Occupational Health, Helsinki b) Uusimaa Regional Institute of Occupational Health, Helsinki
22.	Cordier et al	Grant from National Center Scientific Research (CNRS), Programme, PIREN
321.	Lemasters	Support not stated: PhD dissertation

Table 9: Source of Support - Studies of Spontaneous Abortion in Meta-Analysis

Total Studies = 5

1. Studies supported by government grants or contracts = **0/5**
2. Research units/institutes (support not stated) = **2/5**
3. Support not stated (PhD dissertation) = **1/5**
4. Semiconductor Industry Association = **1/5**
5. Charitable organization = **1/5**

Ref	Authors	Source of Support
11.	Windham et al	Support not stated: a) Special Epidemiology Studies Programme and Air Toxicology and Epidemiological Section, Dept Health Services, Berkeley b) Dept Epidemiology and Maternal and Child Health, School of Public Health, University of California, Berkeley, CA
28.	Lipscomb et al	Support not stated: a) Special Epidemiological Studies Programme b) Hazard Identification and Risk Assessment Branch, Dept of Health Services, Berkeley c) Dept of Mental Health, Cummunity and Administrative Nursing, University of California, San Francisco
233.	Shenker et al	Semiconductor Industry Association
324.	Pinney	Support not stated: PhD dissertation
340.	Eskenazi et al	March of Dimes Reproductive Hazards in the Workplace Grant

Table 10: Results of Studies Comparing Outcomes of Fetuses Exposed or Not Exposed to Organic Solvents

Ref		Exposure		Congenital Defect Yes	No	Total	Chi square	p
9	CR	organic solvents	yes	3	489	492	0.00	0.991
			no	4	492	496		
			total	7	988	988		
12	CCR	organic solvents	yes	23	26	49	2.59	0.107
			no	546	1026	1572		
			total	569	1052	1621		
21	CCR	organic solvent	yes	11	7	18	0.50	0.478
			no	1464	1438	2902		
			total	1475	1475	2950		
22	CCR	organic solvents	yes	29	22	51	2.14	0.144
			no	234	285	519		
			total	263	307	570		
321	CR	styrene	yes	4	68	72	3.79	0.052
			no	13	822	835		
			total	17	890	907		
TOTAL			yes	70	612	682	176.65	0.0001
			no	2261	4100	6354		
			total	2331	4712	7036		

Table 11: Results of Studies Comparing Outcomes of Fetuses Exposed or Not Exposed to Organic Solvents

				Spontaneous Abortion				
Ref		Exposure		Yes	No	Total	Chi square	p
11	CCR	any solvent product	yes	89	160	249	0.99	0.319
			no	272	575	847		
			total	361	735	1096		
28	CR	organic solvent	yes	10	39	49	5.00	0.201
			no	87	854	941		
			total	97	893	990		
233	CP	organic solvents	yes	12	8	20	0.87	0.352
			no	16	21	37		
			total	28	29	57		
324	CR	organic solvents	yes	35	228	263	0.00	0.942
			no	25	166	191		
			total	60	394	454		
340	CP	organic solvents	yes	4	97	101	0.02	0.907
			no	7	194	201		
			total	11	291	302		
TOTAL			yes	150	532	682	4.21	0.04
			no	407	1810	2217		
			total	557	2342	2899		

Table 12: Mantel Haenszel Estimates of Odds Ratios and Confidence Intervals for Case-Control Studies of Fetuses Exposed or Not Exposed to Organic Solvents - Malformations

Ref.	ORi	95% Confidence Interval
12	1.66	0.94 - 2.94
21	1.58	0.61 - 4.08
22	1.61	0.90 - 2.87

Table 13: Risk Ratios and Confidence Intervals for Cohort Studies Comparing Malformation Risk in Fetuses Exposed and Not Exposed to Organic Solvents

Ref.	RRi	95% Confidence Interval
9	0.75	0.17 - 3.40
321	3.72	1.18 - 11.72

Table 14: Mantel-Haenszel Estimates of Odds Ratios and Confidence Intervals for Case-Control Studies of Fetuses Exposed or Not Exposed to Organic Solvents - Spontaneous Abortions

Ref.	ORi	95% Confidence Interval
11	1.18	0.87 - 1.58

Table 15: Risk Ratios and Confidence Intervals for Cohort Studies Comparing Spontaneous Aboriton Risk in Fetuses Exposed and Not Exposed to Organic Solvents

Ref.	RRi	95% Confidence Interval
28	2.52	1.21 - 5.22
233	1.97	0.65 - 5.95
324	1.02	0.59 - 1.77
340	1.14	0.33 - 3.98

TABLE 16

Malformation - Effect Size

Ref	di
9	0.000682
12	0.8000
21	0.0261
22	0.123
321	0.129

All studies: average d=0.071
Case-control: average d=0.076
Cohort: average d=0.064

Spontaneous Abortion - Effect Size

Ref	di
11	0.06
28	0.15
233	0.25
324	0.0094
340	0.012

All studies: average d=0.095
Case-control: d=0.06
Cohort: average d=0.10

Table 17: QUALITY ASSESSMENT

Malformations

Study #	Type	Quality Score: Ernest	Merry	Average	Score
9	C	33/40(0.83)	36/40(0.90)	34.5/40	0.86
12	CC	31/35(0.89)	34/35(0.97)	32.5/35	0.93
21	CC	25/35(0.71)	28/35(0.80)	26.5/35	0.76
22	CC	31/35(0.89)	30/35(0.86)	30.5/35	0.87
321	C	27/40(0.68)	40/40(1.00)	33.5/40	0.84
Total		147/185	168/185	157.5/185	

Spontaneous Abortions

Study #	Type	Quality Score: Ernest	Merry	Average	Score
11	C	39/40(0.98)	39/40(0.98)	39/40	0.98
28	CC	30/35(0.86)	29/35(0.83)	29.5/35	0.84
233	CC	33/35(0.94)	32/35(0.91)	32.5/35	0.93
324	CC	29/35(0.83)	32/35(0.91)	30.5/35	0.87
340	CC	32/35(0.91)	32/35(0.91)	32/35	0.90
Total		163/180	164/180	163.5/180	

Figure 1: Malformations Homogeneity L'Abbe Plot

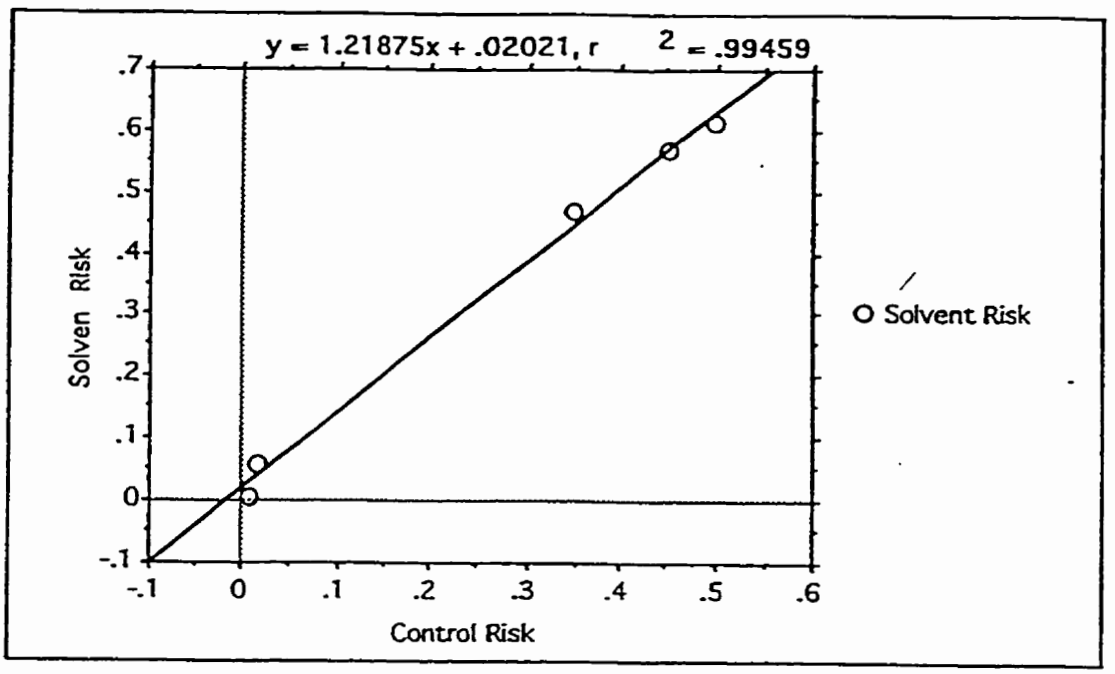


Figure 2: Spontaneous Abortion Homogeneity L'Abbe Plot

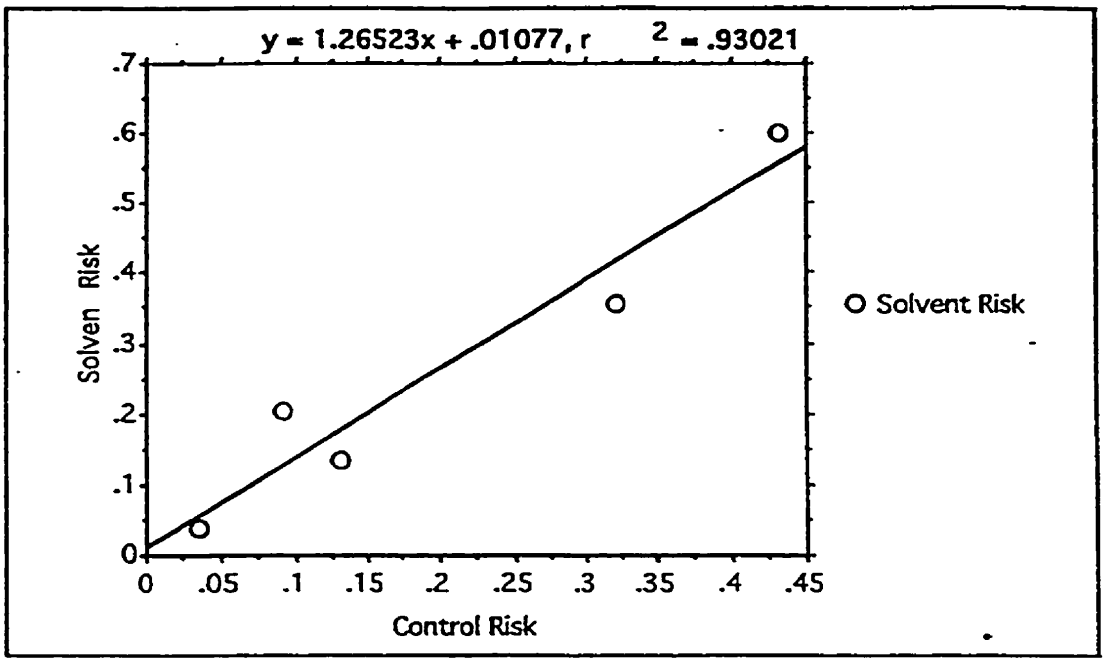


Figure 3: Malformations: Quality Assessment Score Versus Individual Odds Ratio

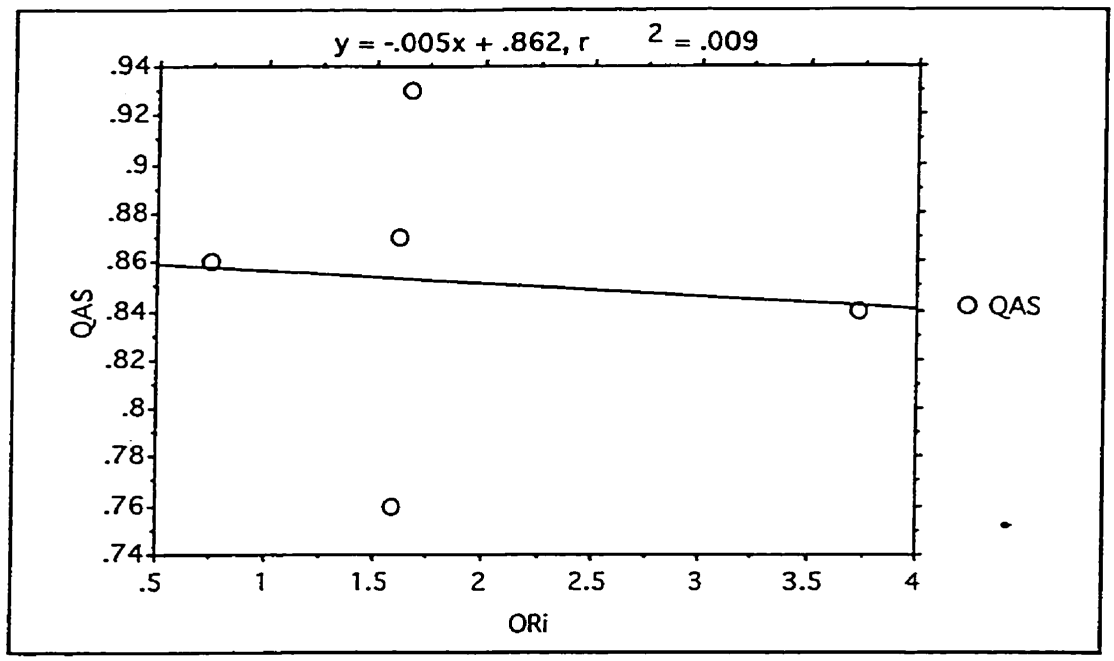
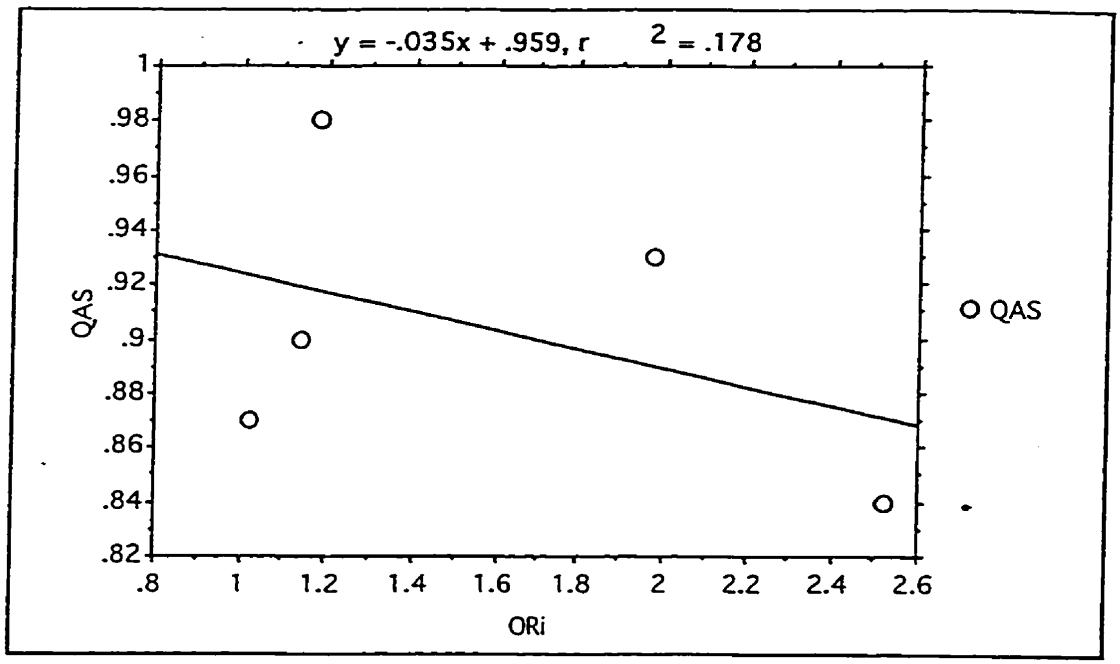


Figure 4: Spontaneous Abortion: Quality Assessment Score Versus Individual Odds Ratio



DISCUSSION

The "true" figure for spontaneous abortions as a proportion of all pregnancies is difficult to estimate because of the methodological problems of identifying abortion. Spontaneous abortions have been divided into clinically recognized and unrecognized abortions. A pregnancy can be clinically recognized at the earliest around 3-5 weeks after conception. Unrecognized spontaneous abortions occur during the period of transportation of the embryo to the uterus, implantation in the uterine lining and post-implantation. Information on the early abortions can only be collected by very sensitive pregnancy assays.

Estimates for clinically recognized spontaneous abortions as a proportion of all pregnancies vary markedly. In ten descriptive studies reviewed by Axelsson (348), the proportion of spontaneous abortions varied from 9% to 15% in different populations. The variation depended not only on the characteristics of the population but on the methods used in the study, i.e. the selection of the study population, the source of pregnancy data, the definition of spontaneous abortion, the occurrence of induced abortions and their inclusion or otherwise in the data. The proportion has been highest in retrospective studies based on interview data (348). The weaknesses of the studies using interviews or questionnaires pertain to the possibility of differential recognition and recall (or reporting) of spontaneous abortions and of differential response. Both exposure and the outcome of pregnancy may influence the willingness of subjects to respond to a study. One advantage of interview data is that it is more likely to provide information on early spontaneous abortion than medical records. However, the validity of information on early abortion which may be difficult to distinguish from a skipped or delayed menstruation has been suspect. Spontaneous abortions which have come to medical attention are probably better defined than self-reported abortions.

The feasibility of using medical records as a source of data depends on the pattern of use of medical facilities in the community and the coverage and correctness of the records. Of concern is the potential selection bias due to differing patterns of use of medical services. The primary determinant for seeking medical care is probably gestational age so that earlier abortions are less likely to be medically recorded than later abortions (348). The advantage of data on medically diagnosed spontaneous abortions, compared to interview data is that the former are independent of an individuals own definition, recognition and reporting.

Evidence of fetal damage or demise from organic solvent levels that are not toxic to the pregnant women is inconsistent in the medical literature. The risk for major malformations and spontaneous abortion from maternal inhalational organic solvent exposure during pregnancy was summarized using meta-analysis. Besides being more objective than the traditional methods of literature review, it has the ability to pool research results from various studies thereby increasing the statistical strength /power of the analysis. This is especially useful in epidemiologic studies, such as cohort studies or case control studies since very often large numbers of subjects are required in order for any problem to be significantly addressed. This is particularly true for teratogenic studies where the frequencies of malformation are often very low.

SPONTANEOUS ABORTION

Five studies were included in the spontaneous abortion analysis. Study size of each paper ranged from n=57 to n=1096. The overall ORs was 1.25 (95% CI: 0.99 - 1.58) which indicates that maternal inhalational occupational exposure to organic solvents is not associated with an increased risk for spontaneous abortion. Study # 28 yielded an odds ratio of 2.52 with a 95% confidence interval of 1.21 - 5.22. This large spread in the confidence interval range may be due to the small number of

subjects versus controls (49 versus 941) in estimating the effect of solvent exposure in pregnancy and outcome of spontaneous abortion.

When studies were analyzed according to study type the summary odds ratio for cohort studies was 1.39 (95% CI: 0.95 - 2.04). For the case control study the summary odds ratio was 1.18 (95% CI: 0.87 - 1.58). Their combinability seems justified on the basis of the lack of finding heterogeneity among the results.

Tests for homogeneity including that used in this study have been criticized for the lack of power (575). Hence a graphical approach for examining homogeneity was conducted as suggested by L'Abbe. This too showed a relatively homogenous group of studies.

Publication bias is an issue that meta-analysts must consider. It is the tendency for statistically significant studies to be submitted and accepted for publication in preference to studies that do not produce statistical significance. This does not appear to be the case for organic solvent exposure and spontaneous abortions. For the majority of papers examined in this analysis, there was no significant adverse risk associated with organic solvents.

Traditionally, a power analysis would be conducted to determine the number of subjects or in this situation the number of "studies" that need to be added to produce a significant result. Munroz and Rosner (602) and Wittes (603) have presented a method for the calculation of power for 2X2 tables. An underlying assumption for these statistical methods is that there must be a trend in the positive direction i.e., risk ratio must be greater than unity (1). Ideally this test would be used for approximating the power of the Mantel-Haenszel procedures. Given this limitation, an alternative power analysis has been suggested by Orwin.

In order to perform a power analysis, using this method, effect sizes must be calculated from the summary statistic. Effect sizes represent the magnitude of the relationship between two variables. Unlike statistical significance, which is directly related to sample size, an effect size may be thought of as significance without the

influence of sample size. In other words, effect size represents the "true" impact of an intervention. Cohen has determined that an effect size d=0.2 is considered small, 0.5 is medium and 0.8 is large (604).

The number of studies with a medium effect size (d=0.5) required to be added to produce a significant result was calculated using Orwin's approach. Orwin has presented a formula which is a simple mathematical manipulation that can be used to determine how many studies of a given effect size are required to bring a calculated effect size to any given value. The result from this power analysis indicates that one would have to obtain 2 studies with a medium effect size (0.5) to bring this study's overall effect size (d=0.095) to a small effect size of 0.2. Similarly, 5 articles with an effect size of d=0.3 are needed to bring the study's overall effect size to 0.2. The largest effect size in the spontaneous abortion analysis was d=0.2. None of the acceptable studies achieved such a large effect size as 0.5. It may be improbable because one would expect that such results would undoubtedly have been published. Unfortunately, no statistical test yet exists to precisely determine such a probability and one must therefore exercise judgment.

There are some considerations to bear in mind when interpreting results from the spontaneous abortion meta-analysis:

1. Environmental exposure in pregnancy is seldom an isolated phenomenon, therefore, analysis of human abortion data may require stratification for a number of factors depending on the intended focus of the analysis. Such factors may include environmental influences, age, obstetrical history, race, personal habits such as alcohol intake and smoking, trimester of drug exposure, duration of exposure, frequency of exposure or presence of other disease states. Previous pregnancies may be important because of the phenomena of recurrent spontaneous abortion (578). If one wished to assess the risk of spontaneous abortion due to organic solvent

exposure in a certain subgroup of patients, then 2X2 tables would need to be constructed using only those data provided they exist in the primary literature and the analysis conducted as described.

2. Mothers often are exposed to or take more than one chemical compound in pregnancy and there were multiple exposures present in both cases/cohorts and controls. The possible confounding effects of a uterine stimulant exposure must be kept in mind in such an analysis. The argument against this would be that the control group would be similarly exposed and thus cancel out the effects of the confounders.

3. This paper addresses the use of organic solvents in pregnancy. Organic solvents is a very broad term that includes many classes of chemicals. There may still exist rates of abortion higher than the value reported with certain groups of solvents. However, a detailed analysis of classes of solvents is in order to incriminate a particular solvent. Not all of the studies have examined the same groups of solvents in terms of both extent and range of solvents as well as frequency and duration of exposure. Hence it would be very difficult to obtain any clear estimate of risk for a given solvent given the limited number of studies available.

To improve further studies of this type, a call for better reporting in particular to industrial hygiene assessment in papers is in order as it is difficult to judge the 'representativeness' of a summary effect if the populations being pooled seem to be heterogeneous.

MAJOR MALFORMATIONS

In this meta-analysis, major malformation was defined by Heinonen as "potentially life threatening or a major cosmetic defect" (577). In the general population there is a 1-3% baseline risk for major malformations.

Five studies were included in the malformation analysis. Study size of each paper ranged from n=570 to n=2950. The overall summary odds ratio was 1.64 (95% CI: 1.16 - 2.30) which would indicate that maternal inhalational occupational exposure to organic solvents is associated with an increased risk for major malformations. Study # 321 yielded an odds ratio of 3.72 (95% CI: 1.18 - 11.72). This large spread in the confidence interval range may be due to the small number of subjects in exposed group versus the control group (72 versus 835).

Tests for homogeneity including the graphical approach showed a relatively homogeneous group of studies. When studies were analyzed according to study type the summary odds ratio for cohort studies was 4.74 (95% CI: 2.08 - 10.81). The summary odds ratio for case control studies was 1.62 (95% CI: 1.12 - 2.35). Their combinability remains justified on the basis of the lack of finding heterogeneity among the results.

Publication bias is the tendency for statistically significant studies to be submitted and accepted for publication in preference to studies that do not produce statistical significance. This may be the case for solvent exposure and major malformations. Determining the extent of possible publication bias is not unlike power analysis for nonsignificant results. Each provides some quantitative measure of the magnitude of the findings with respect to disproving them and requires judgment for interpretation. A formula for estimating the significance of the file drawer problem when a meta-analysis produces significant results would be Orwin's formula as discussed for the previous power analysis.

Orwins's formula can be used to determine how many studies of a given effect size are required to bring a calculated effect size to any given value. The result from this file drawer analysis indicates that one would have to obtain 2 articles with a small effect size (d=0.001) to bring the study's overall effect size (d=0.071) to a smaller effect size of 0.05. One of the acceptable studies achieved such a small effect size. The smallest effect size in the study was d=0.000682 (Study #1). It would therefore seem probable to have some studies stored away in file drawers with very small effect sizes (lack of statistical significance). Unfortunately, no statistical test yet exists to precisely determine such a probability and one must therefore exercise judgment.

There are some considerations to bear in mind when interpreting results from the malformation meta-analysis:

1. Environmental exposure in pregnancy is seldom an isolated phenomenon, therefore, analysis of human teratogenicity data may require stratification for a number of factors depending on the intended focus of the analysis. Such factors may include environmental influences, age, obstetrical history, race, personal habits such as alcohol intake and smoking, trimester of drug exposure, duration of exposure, frequency of exposure or presence of other disease states. If one wished to assess the risk of teratogenicity due to organic solvent exposure in a certain subgroup of patients, then 2X2 tables would need to be constructed using only those data provided they exist in the primary literature and the analysis conducted as described.

2. Mothers often are exposed to or take more than one chemical compound in pregnancy and it is possible that there were multiple exposures present in both cases/cohorts and controls. The possible confounding effects of a teratogenic exposure must be kept in mind in such an analysis. The argument against this

would be that the control group would be similarly exposed and thus cancel out the effects of the confounders.

3. This paper addresses the use of organic solvents in pregnancy. Organic solvents is a very broad term that includes many classes of chemicals. There may still exist rates of malformation higher than the value reported with certain groups of solvents. However, a detailed analysis of classes of solvents is in order to incriminate a particular solvent. Not all of the studies have examined the same groups of solvents in terms of both extent and range of solvents as well as frequency and duration of exposure. Hence it would be very difficult to obtain any clear estimate of risk for a given solvent given the limited number of studies available.

To improve further studies of this type, a call for better reporting in particular to industrial hygiene assessment in papers is in order as it is difficult to judge the 'representativeness' of a summary effect if the populations being pooled seem to be heterogeneous.

4. The malformations listed in each of the papers seems to reflect a diverse range of anomalies. One might expect to notice a particular trend in malformations between studies however this does not appear to be the case.

Certain factors should be kept in mind when evaluating the results such that a number of studies were case control in design. Certain factors inherent in this study design may affect the interpretation of their results, including recall of events during pregnancy, selection of samples based on volunteer reporting and a change in the knowledge over time regarding factors considered to significantly affect the fetus. Mothers of malformed children may understandably report exposure more often than mothers of healthy children. The recall of the exact name of the chemical, amount of exposure, starting and stopping date of exposure are also

difficult to establish retrospectively. Recall may be affected by the method of questioning; when asked open ended questions, women may not recall details as well as when questioned with respect to specific chemical exposure. As a result, there could be systematic bias toward reporting exposure.

It is important to consider the criteria or "proof" for human teratogenicity as put forth by Shepard (612):

1. *Proven exposure to agent at crititcal time(s) in prenatal development (prescriptions, physicians' records, dates).*

One of the inclusion criteria for this meta-analysis, with malformations as the outcome of exposure, was first trimester exposure to organic solvents.

2. *Consistent findings by two or more epidemiologic studies of high quality*

   a) *control of confounding factors*
   b) *sufficient numbers*
   c) *exclusion of positive and negative bias factors*
   d) *prospective studies if possible*
   e) *relative risk of six or more*

When this happens it is unlikely that methodological problems or systematic biases can influence the results of the studies conducted in different contexts and different study designs. The studies included in this meta-analysis usually controlled for such items as geographical location and date of birth, however, other potential confounding factors such as maternal age, alcohol, and smoking that could lead to subsequent problems in outcome presentation were not consistently reported.

In addition, this meta-analysis included studies that were contained within large databases spanning many years. The majority of information about

occupational exposure in general during pregnancy originates from Scandinavia, namely, the Institute of Occupational Health in Helsinki. For example, Finland monitors spontaneous abortions through the spontaneous abortion registry. The registry contains all information about women who were hospitalized with spontaneous abortions covering approximately 90% of all spontaneous abortions in Finland. Finland also monitors births via the Finnish Register of Congenital Malformations. All new mothers in Finland are interviewed during their first prenatal visit, at 3 months post-delivery, at Maternity Care Centres located in every province throughout Finland.

When scanning the literature, there are no studies that prospectively examine occupational exposure to organic solvents during pregnancy and pregnancy outcome with regard to malformations. The studies are retrospective, either case-control or cohort in design. In contrast, however, there are a number of studies that prospectively examine occupational exposure during pregnancy and pregnancy outcome with regard to spontaneous abortion.

In all the studies there was an attempt to ascertain the occupational exposure by an industrial hygienist who blindly assessed the group exposure information. In addition, the individual studies included in the meta-analysis did not obtain an odds ratio or relative risk of 6.0 or more with a significant 95% confidence interval.

3. *Careful delineation of the clinical cases. A specific defect or syndrome, if present, is very helpful.*

If the teratogen is associated only to one or a few specific birth defects, the possibility of a spurious association becomes smaller. In this meta-analysis, the malformations were variable with no specific trend apparent.

4. *Rare environmental exposure associated with rare defect.*

5. *Teratogenicity in experimental animals important but not essential.*

Many organic solvents are teratogenic and embryotoxic in laboratory animals, depending on specific solvent, dose, route of administration, and animal species. Malformations described include hydrocephaly, exencephaly, skeletal defects, cardiovascular abnormalities and blood changes. Other problems include poor fetal development and neurodevelopmental deficits. In some of the studies exposure levels were high enough to induce maternal toxicity.

Acetic anhydride induced multiple malformations in mouse fetuses when given intraperitoneally for 4-day periods in gestation (362). Acetonitrile caused brain and rib defects in hamster embryos when administered by inhalation (398).

Benzene was not teratogenic in rats by the inhalation route (94). In mice, cleft palate and jaw defects were reported upon parenteral injection (123), while administration of benzene by either the oral or inhalational route did not elicit malformations (157, 129). Benzene was embryotoxic in rabbits when given by inhalation but also it did not induce congenital malformation (129).

Toluene produced only decreased fetal weight and skeletal retardation and no malformations in rats when administered by inhalation (99) nor was it teratogenic in mice by this route (98). Oral administration of toluene to mice induced cleft palate (157).

Xylene itself was not teratogenic in the rat by inhalation (98). However, isomers of xylene were active in rodents, although the results depended upon route. For instance, the m-, o-, and p-xylene forms were nonteratogenic by the inhalation route in rats (164, 100) and teratogenic by the oral route in mice (114). A xylene mixture (m-, o-, p- and ethyl forms) induced cleft palate and wavy ribs in mice following oral administration during organogenesis (110).

6. The association should make biologic sense.

When a chemical or any other environmental factor caused a malformation in the experimental animals and/or the biological mechanism is understood or reasonably envisaged, the observation of an association in humans becomes more plausible. However, the necessity that a biologically plausible association must exist before any association can be regarded as causal, indicates the distinction between statistical significance and biological significance in epidemiologic studies. Although the statistical association must be present before any relationship can be said to exist, only biological plausible associations can result in "biological significance".

The mechanisms by which many solvents exert their toxicity are unclear and may vary from one solvent to another. Halogenated hydrocarbons such as carbon tetrachloride may generate free radicals (34). Simple aromatic compounds such as benzene may disrupt polyribosomes, whereas some solvents are thought to affect lipid membranes and to penetrate tissues such as the brain (618).

In 1979 a syndrome of anomalies (hypertonia, scaphocephaly, mental retardation and other CNS effects) was suggested in two children in a small American Indian community where gasoline sniffing and alcohol abuse are common. Four other children had similar abnormalities, however, in these cases it was impossible to verify gasoline sniffing. Also, it is unclear what was the contribution of the lead in the gasoline or the alcohol abuse in producing these abnormalities. It is important to remember that the mothers in many of these cases showed signs of solvent toxicity indicating heavy exposure. This is not the case in most occupational exposures during pregnancy. While fetal toxicity is biologically sensible in cases of intoxicated mothers, the evidence of fetal damage from levels that are not toxic to the mother is scanty, inconsistent or missing.

7. Proof in an experimental system that the agent acts in an unaltered state. Important information for prevention.

Several lists of criteria for human teratogenicity have included the dose (or concentration) response relationship (613, 614, 615). Although a dose response may be considered essential in establishing teratogenicity in animals it is extremely uncommon to have sufficient data in human studies. Another criterion which is comforting to have but not very often fulfilled is biologic plausibility for the cause. Shepard states that at present there is no biologically plausible explanation for thalidomide embryopathy and that at least one half of all human teratogens do not fit this criterion (612).

Bertollini et al also discuss the criteria of causality to be met to conclude on the teratogenicity of a given substance (616). The list is similar to the previous criteria of Shepard (612) with one addition:

8. Strength of the association

The larger the value of the relative risk, the less likely the association is to be spurious (617). If the association between a teratogen is weak and the relative risk small (i.e. range 1.1-2.0), it is possible to think that the association is indeed due to unknown confounding factors and not to the teratogen under study. However, weak associations may be due to misclassification of exposure or disease. They may also indicate an overall low risk but the presence of a special subgroup at risk of disease within the exposed group.

The limitations discussed addressed the lack of consistency across studies in reporting information that would be essential in understanding whether the studies being combined are similar. These would be factors that can influence the type of exposure or outcome that was recorded. Information regarding: **1)** whether proper control /adjustment was made for biases that frequently occur in epidemiologic

studies or **2)** whether confounding variables could have influenced outcome and **3)** whether observers were blinded to the exposure status of subjects. These descriptive details were not mentioned consistently across the studies or the extent to which some researchers reported these concerns varied across the studies examined.

The results of this qualitative component are similar with the findings of Emerson that investigated whether a quality scoring system could have a direct use in adjusting the summary estimates of a treatment difference (624). When analyzing the relationship of quality scores to treatment differences in meta-analyses of 7 groups of controlled clinical trials, including a total of 107 studies, Emerson found no relationship between treatment differences and overall quality score. Seto (623) similarly found no association between quality of studies and odds ratio. This supports Glass' theory that no researcher would intentionally conduct a poorly designed study and that all studies, as long they fit a stringent inclusion and exclusion criteria, should be included in the meta analysis. However, there is a value in a quality scoring system for epidemiological studies. It contributes to improvement of research practice and reporting practice. It can also provide guidance and feedback to investigators who are aiming to establish their own research.

CONCLUSION

The meta-analysis examining organic solvent use in pregnancy did not appear to find a positive association between organic solvent exposure and spontaneous abortions (ORs = 1.25, confidence interval 0.99 - 1.58). The results from the meta-analysis examining organic solvent use in the first trimester of pregnancy and major malformations indicate that solvents are associated with an increased risk for major malformations (ORs = 1.64, confidence interval 1.16 - 2.30). However, the significance of the results with regard to malformations warrant further studies, namely a *prospective* analysis of organic solvent exposure and pregnancy outcome. Meta-analysis can be a key element for improving individual research efforts and their reporting in the literature. This is particularly important with regard to an estimate of dose in occupational studies as better reporting of the quantification of solvent exposure is needed in the literature. Improvements such as this will further enhance the role of meta-analysis in helping clinicians and policymakers answer clinical questions.

APPENDIX A

INCLUSION CRITERIA	EXCLUSION CRITERIA
Any language	animal study
Human study	case report, letters, editorials
Maternal organic solvent exposure (inhalational)	review articles
Outcome = major malformation (Heinonen)	studies that do not permit
=spontaneous abortion (<20 wks)	extraction of data for 2X2
1st trimester pregnancy exposure	tables
Nonexposed control	

APPENDIX B

Malformations of the Central Nervous System (CNS)

Anencephaly	major
Encephalocele	major
Meningomylocele	major
Spina bifida without CNS involvement	minor
Spina bifida with meningomylocele	major
Absent corpus callosum	major
Hydrocephaly	major
Microcephaly	major
Hypoplasia/atrophy brain -secondary	major
Miscellaneous brain abnormalities	major
Malformed medulla	major
Craniosynostosis	major
Macrocephaly	major
Absence olfactory nerve/arhinencephaly	major
Cerebral hypoplasia-primary	major
Porencephaly/hydrancephaly	major
Anomalies pituitary	major
Rachischisis/cranioschisis	major
Miscellaneous sinus tract abnormalities	minor
Arnold Chiari/Dandy Walker	major
Atrophy/hypoplasia optic nerve	major
Craniospinal fusion defects without anencephaly	major
Any cranial nerve malformation	major
Any brain malformation	major
Any spinal malformation	major
Craniospinal fusion defects with anencephaly	major

Malformations of the Cardiovascular System (CVS)

Any atrial septal defect (secundum or primum)	major
Any ventricular septal defect (open or closing)	major
Atrioventricular canal	major
Aortic valve malformation (stenosis or atresia)	major
Pulmonic valve malformation	major
Mital valve malformation	major
Tricuspid valve malformation	major
Any malposition of great vessels (union)	major
Transposition of great arteries	major
Anomalous venous drainage	major
Abnormalities of coronary arteries, isolated	major
Ductus arteriosus persistens	major

Any coarctation of aorta-pre-ductal or post-ductal	major
Truncus arteriosus	major
Vascular ring	major
Coarctation of aorta-pre-ductal	major
Coarctation of aorta-post-ductal	major
Abnormalities of coronary arteries	major
Endocardial fibroelastosis	major
Endomyocardial fibrosis	major
Single atrium	major
Single ventricle	major
Tetralogy of Fallot	major
Aortic and mitral valve atresia	major
Ventricular septal defect and pulmonic stenosis (VSD open or closing and pulmonic stenosis or peripheral pulmonic stenosis)	major
Abnormalities of coronary arteries, multiple	major
Truncus arteriosus, isolated	major
Truncus arteriosus, multiple	major
Single ventricle, isolated	major
Single ventricle, multiple	major
Atrial septal defect-secundum	major
Atrial septal defet-secumdum, isolated	major
Atrial septal defect-secundum, multiple	major
Atrial septal defect-primum	major
Atrial septal defect-primum, isolated	major
Atiral septal defect-primum, multiple	major
Any atrial septal defect-secundum or primum, isolated	major
Any atrial septal defect-secundum or primum, multiple	major
Ventricular septal defect (open)	major
Ventricular septal defect (open), isolated	major
Ventricular septal defect (open), multiple	major
Ventricular septal defect-spontaneously closing	major
Any ventricular septal defect (open or closing), isolated	major
Any ventricular septal defect (open or closing), multiple	major
Atrioventricular canal, isolated	major
Atrioventricular canal, multiple	major
Aortic stenosis	major
Aortic stenosis, isolated	major
Aortic stenosis, multiple	major
Vascular ring, isolated	major
Vascular ring, multiple	major
Hypoplasia left venricle	major
Left vena cava	minor
Wolff-Parkinson-White syndrome	minor
Anomalous right subclavian artery	minor
Hypoplasia left atrium	major
Hypoplasia cordis	minor
Endocardial disease (union)	major

Aortic insufficiency	major
Conus arteriosus syndrome	major
Endocardial cushion defect	major
Aortic valve malformation (stenosis or atresia), isolated	major
Aortic valve malformation (stenosis or atresia), multiple	major
Pulmonic valvular or unspecified strenosis	major
Pulmonic valvular or unspecified stenosis, isolated	major
Pulmonic vavular or unspecified stenosis, multiple	major
Peripheral pulmonic stenosis	major
Peripheral pulmonic stenosis, isolated	major
Peripheral pulmonic stenosis, multiple	major
Pulmonary atresia	major
Pulmonaru atresia, isolated	major
Pulmonary atresia, multiple	major
Tricuspid valve malformation, isolated	major
Pulmonic valve malformation, isolated	major
Pulmonic valve malformation, multiple	major
Mitral insufficiency	major
Tricuspid valve malformation, multiple	major
Rare single malformation	minor
Hypoplastic left heart syndrome	major
Transposition of great arteries, isolated	major
Transposition of great arteries, multiple	major
Double outlet of right ventricle	major
Double outlet of right ventricle, isolated	major
Double outlet of right ventricle, multiple	major
Hypoplasia pulmonary artery	minor
Any malposition of great vessels, isolated	major
Any malpostion of great vessels, multiple	major
Ductus arteriosus persistens, isolated	major
Ductus arteriosus persistens, multiple	major
Coarctation of aorta-prepductal, isolated	major
Coarctation of aorta-pre-ductal, multiple	major
Any coarctationof aorta (pre-ductal or post-ductal), isolated	major
Any coarctation of aorta (pre-ductal or post-ductal), multiple	major

Malformations of the Musculoskeletal System

Polydactyly	minor
Absence of limb or part thereof	major
Hypoplasia of limb or part thereof	major
Syndactyly	major
Arthrogryposis	major
Anomalies of vertebrae	minor
Hemivertebrae	major
Congenital dislocation of hip	major
Hemimelia/phocomelia	major
Muscle absence/atrophy/hypoplasia	major
Absence/atrophy/hypoplasiapectoralis	major
Absence/atrophy/hypoplasia rectus abdominis	major
Micrognathia/hpyoplastic jaw	major
Miscellaneous foot abnormalities	minor
Anomalies of ribs/sternum	minor
Abnormal face/skull	major
Abnormal implantation/deformed toes	minor
Webbed neck	minor
Other musculoskeletal malformatins	major
Some muscle absence/atrophy/hypoplasia	major

Malformations of the Respiratory Tract

Laryngeal/tracheal malacia	major
Malformations of epiglottis/larynx/bronchi	major
Malformatins of thoracic wall	major
Malformations of diaphragm	major
Diaphragmatic hernia	major
Hypoplasia/agenesis lung	major
Bilobed lung	minor
Choanal atresia	major
Hiatal hernia	major
Malformed lung	minor
Anomalies of teeth	minor
Other respiratory malformations	major
Cleft lip only	major
Co-existent cleft lip and palate	major
Cleft lip with or without cleft palte	major
Cleft palate only	major
Some epiglottis/bronchi malformations	major

Malformations of the Gastrointestinal Tract

Omphalocele	major
Anal atresia	major
Tracheo-esophageal fistula	major
Malrotation	minor
Hirschsprung's disease	major
Duodenal atresia	major
Other gastrointestinal malformations	major
Other hernias	minor
Anomalies of pancreas	major
Anomalies of liver	major
Anomalies of gallbladder	major
Pyloric stenosis	major
Meckel's diverticulum	minor
Atresia/agenesis colon	major
Atresia/hypoplasia small intestine	major
Anomalous shaped/lobation of liver	minor
Biliary atresia	major
Atrophy/hypoplasia intestine	major
Accessory spleen	minor
Umbilical hernia	minor
Asplenia	major
Anomalies of pancreas/gallbladder	major

Malformations of Genitourinary System

Hypospadias	minor
Polycystic kidney	major
Single kidney	major
Hypoplastic kidney	major
Horseshoe kidney	major
Other kidney malformations	major
Duoble ureter	major
Absent ureter	major
Stenotic ureter	major
Hypoplasia penis	major
Abnormal testes	major
Malformed uterus/fallopian tubes	major
Abnormal ovary	major
Rectal fustula	major
Malposition/ectopic kidney	major
Double collecting system	major
Mullerian malfusion	major
Malformations of bladder/ureter	major
Hydronephrosis	major

Hydroureter	major
Obstructive uropathy	major
Ambiguous genitalia	major
Hydrocele	major
Malformations of male genitalia-minor	minor
Malformations of female genitalia-major	major
Malformations of female genitalia-minor	minor
Some uterine malformations	major
Some double collecting malformations	major

Malformations of Eye and Ear

Anophthalmia/microphthalmia	major
Coloboma	minor
Cataract	major
Glaucoma/buphthalmos	major
Corneal opacity	major
Other eye malformations	major
Absent/abnormal external meatus	major
Pre-auricular skin tag	minor

Syndromes

Down	major
Situs inversus/dextrocardia	major
Hypertrophy/enlarged adrenal	major
Hypoplasia/atrophy adrenal	major
Anomalies thyroid	major
Other adrenal syndromes	major
Adrenogenital	major
Pierre Robin	major
Achondroplasia	major
Caffey's	major
Albinism	major
Inborn errors metabolism	major
Other syndromes	major
Turner's	major
Other trisomies	major
Any chromosomal	major
Klinefelter's	major

APPENDIX C

Malformations

	A	B	C	D	a/(a+b)	c/(c+d)	A+B=n1	C+D=n0	A+C=m1
	3	489	4	492	0.006097	0.008064	492	496	7
	23	26	546	1026	0.469387	0.347328	49	1572	569
	11	7	1464	1468	0.611111	0.499317	18	2932	1475
	29	22	234	285	0.568627	0.450867	51	519	263
	4	68	13	822	0.055555	0.015568	72	835	17
SUM	70	612	2261	4093			682	6354	2331
AVG	14	122.4	452.2	818.6	0.342155	0.264229	136.4	1270.8	466.2
STD	10.35374	184.4154	542.9417	413.7978	0.258800	0.211876	178.6332	917.1419	544.4595

B+D=m0	Ni A+B+C+D	1/a..1/d	absAD-BC	nmnm/n-1	χ^2	ORi	LLi	ULi
981	988	0.587410	196	1697839.	0.000115	0.754601	0.168004	3.389328
1052	1621	0.084745	73813872	28461750	2.593441	1.662299	0.939528	2.941090
1475	2950	0.235130	19580625	38935498	0.502899	1.575722	0.609147	4.076026
307	570	0.087719	8020224	3755946.	2.135340	1.605477	0.898452	2.868887
890	907	0.342845	3804450.	1003990.	3.789328	3.719457	1.180500	11.71906
4705	7036							
941	1407.2							
375.1357	842.9442							

χ^2 MH = 7.476769 MH - OR = 1.637276

χ^2 uncor = 7.985832 95% CI

UL Miet = 2.304797

LL Miet = 1.163085

	AD/Ni	BC/Ni	E(Ai) n1m1/Ni	V(Ai)	Homogeneity wi	lnORi	ln2ORi	
	1.493927	1.979757	3.485829	1.739333	1.702386	-0.28156	0.079279	
	14.55768	8.757557	17.19987	10.83167	11.79997	0.508201	0.258268	
	5.473898	3.473898	9	4.474059	4.252957	0.454713	0.206764	
	14.5	9.031578	23.53157	11.56031	11.39996	0.473421	0.224127	Homogen. χ^2 = 2.975177
	3.625137	0.974641	1.349503	1.220436	2.916765	1.313577	1.725486	df = 4
Sum:	39.65064	24.21743	54.56678	29.82581	32.07204	2.468348	2.493927	p = 0.561

APPENDIX D

Spontaneous Abortion

	A	B	C	D	a/(a+b)	c/(c+d)	A+B=n1	C+D=n0	A+C=m1
	89	160	272	575	0.357429	0.321133	249	847	361
	10	39	87	854	0.204081	0.092454	49	941	97
	12	8	16	21	0.6	0.432432	20	37	28
	35	228	25	166	0.133079	0.130890	263	191	60
	4	97	7	194	0.039603	0.034825	101	201	11
SUM	150	532	407	1810			682	2217	557
AVG	30	106.4	81.4	362	0.266839	0.202347	136.4	443.4	111.4
STD	31.324111	79.96649	99.35109	306.7096	0.196300	0.149863	101.1406	373.6638	128.2070

B+D=m0	Ni A+B+C+D	1/a..1/d	absAD-BC	nmnm/n-1	χ^2	ORi	LLi	ULi
735	1096	0.022901	50509449	51104974	0.988347	1.175896	0.874081	1.581924
893	990	0.138306	21641104	4038430.	5.358790	2.516946	1.214255	5.217204
29	57	0.318452	9120.25	10730	0.849976	1.96875	0.651381	5.950396
394	454	0.078981	13689	2621430.	0.005221	1.019298	0.587595	1.768171
291	302	0.408321	2916	215892.0	0.013506	1.142857	0.326636	3.998708
2342	2899							
468.4	579.8							
310.3028	400.2611							

χ^2 MH = 3.197493
χ^2 uncor = 3.423039

MH - OR = 1.247944
95% CI
UL Miet = 1.577983
LL Miet = 0.986934

	AD/Ni	BC/Ni	E(Ai) n1m1/Ni	V(Ai)	Homogeneity wi	lnORi	ln2ORi
	46.69251	39.70802	82.01551	42.54436	43.66515	0.162030	0.026253
	8.626262	3.427272	4.801010	4.120426	7.230331	0.923046	0.852014
	4.421052	2.245614	9.824561	3.302554	3.140186	0.677398	0.458869
	12.79735	12.55506	34.75770	12.71823	12.66119	0.019114	0.000365
	2.569536	2.248344	3.678807	2.367133	2.449053	0.133531	0.017830
Sum:	75.10672	60.18432	135.0775	65.05271	69.14592	1.915121	1.355333

Homogen. c2 = 4.884736
df = 4
p = 0.300

APPENDIX E

Article #

Quality Ratings
1. not at all/ unknown
2. partial, incomplete
3. satisfactory
4. good
5. exceptional

A. SUBJECT SELECTION _____ QUALITY RATING _____
1 2 3 4 5

Case
All mothers who were exposed to organic solvents
in a defined segment of the population/or all children
with a given outcome in a defined population
population: medical care facility or health registry
exposure: given quantity and frequency outcome:
defined malformation (major vs minor)

1. selection of cases/cohort_____

2. description of acceptance criteria used to identify
   subjects_____

Control
All mothers exposed to something other than
investigated exposure (solvents) or children with an
outcome other than the one of interest
Used as a comparison group with the cases

1. selection of controls_____

2. comparability: are mothers of other children with
   birth defects being compared or are mothers who
   were also exposed to other exposures in pregnancy
   being compared_____

B. CONFOUNDERS _____

eg. condition, age, alcohol, smoking that could lead
to subsequent problems in outcome presentation

1. method: exclusion from study or matched pairs_____

2. matching (applicable for only cohort studies)_____

C. FOLLOW-UP _____
defined measurement variable of interest:
A. outcome- major malformation vs minor
malformation/spontaneous abortion at 20 wks.
B. exposure- defined quantity and frequency
collected by blinded assessors and corroborated
with external sources.

1. method of follow-up: ie. blinding_____

2. data collection - data was corroborated
   with an external source
   ie: physician/chart/registry_____

APPENDIX F

META-ANALYSIS CALCULATIONS AND FORMULAE

Significance of individual 2X2 tables

	outcome		
exposure	disease	no disease	total
yes	A	B	n1
no	C	D	n0
total	m1	m0	N

Significance testing of individual 2X2 tables

$$\text{Chi square} = (n-1)\frac{[|ad-bc|-n/2]^2}{n1n0m1m0}$$

Testing for homogeneity

$$\text{Mantel-Haenszel Chi Square} = \frac{S(w*\ln^2 OR)-(S(w*\ln OR^2))}{Swi}$$

where $w = 1/(1/A+1/B+1/C+1/D)$

Calculation of summary odds ratio

$$ORs = \frac{S(ad/n)}{S(bc/n)}$$

Orwin's formula

$$Nfs = No(do-dc)/(dc-dfs)$$

where Nfs is the number of studies of a given effect size (dfs) required to be added to No, the existing number of studies having effect size do, to produce an overall effect size of dc

Effect size

$$di=[4c^2/(Ni-c^2)]^{1/2}$$

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IMAGE EVALUATION
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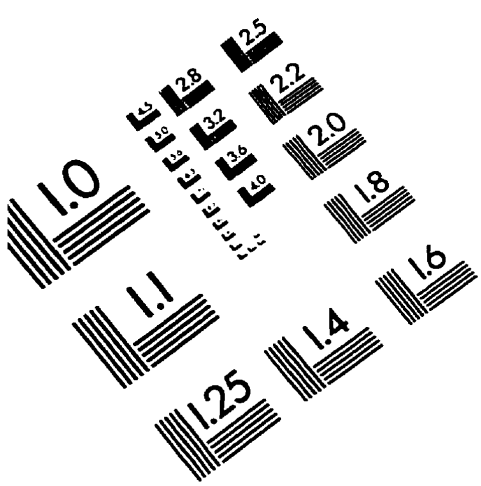

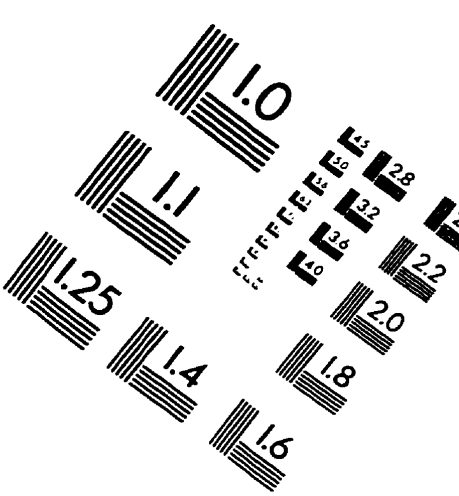

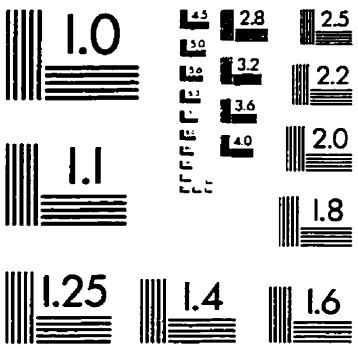

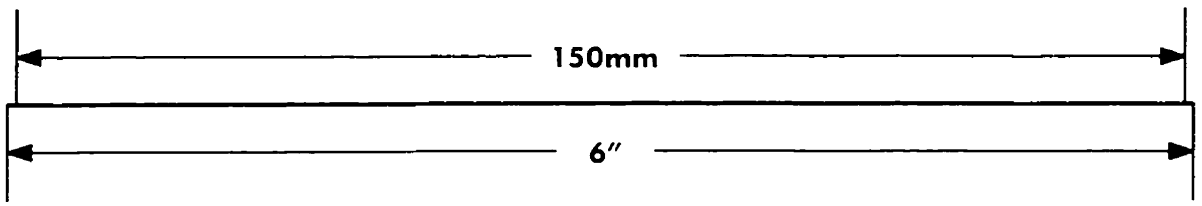

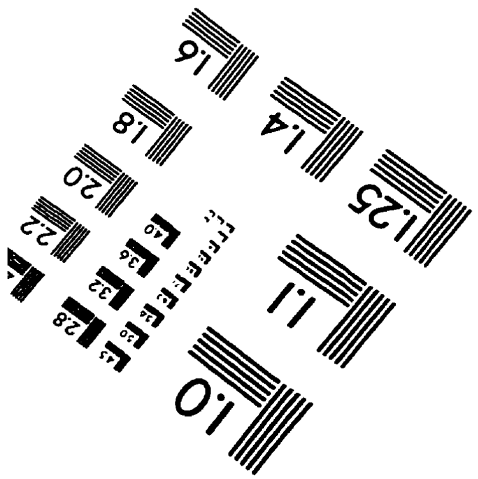

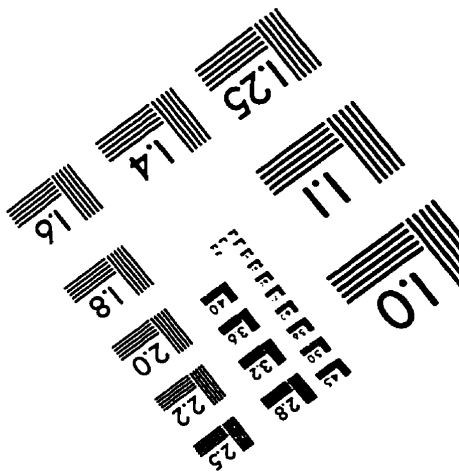

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