FINAL

Meta-Analysis and Causal Inference: A Case Study of Benzene and Non-Hodgkin's Lymphoma

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Abstract

Meta-analysis is an important method in the practice of occupational epidemiology, with a legitimate but limited role to play in causal inference. Meta-analysis provides an assessment of consistency—one of several classic causal criteria—through tests of heterogeneity and an assessment of differences across studies. It may also provide an increase in the precision of effect estimates. Causal inference, however, involves much more: strength, dose-response, and biological plausibility, to name only the most commonly used criteria. Causal claims, therefore, should not emerge from meta-analyses as such. A recent meta-analysis of epidemiological studies of benzene exposure and non-Hodgkin lymphoma (NHL), however, does exactly that. Using studies from a previous narrative review in which the authors made no causal claim, the same authors performed a meta-analysis and concluded that it represented new evidence that benzene causes NHL. Despite a lack of consistency (i.e significant heterogeneity), weak associations, no evidence of dose-response, no effort to provide an assessment of biological plausibility, and no new epidemiological evidence, the authors, nevertheless, changed their conclusion from association to causation. Using case study as an illustrative platform, this commentary provides cautionary and critical comments about the use of meta-analysis and causal inference in occupational epidemiology.

Introduction

In early 2007, investigators from the School of Public Health at the University of California, Berkeley, published a comprehensive review of the epidemiologic evidence on benzene and non-Hodgkin's lymphoma (NHL).[1] They concluded that "the evidence supports an association between occupational benzene exposure and NHL (p. 385)." One year later, the same investigators, plus one, published a meta-analysis of benzene and NHL using the same literature search strategy, and concluded that their study provided new evidence that benzene causes NHL.[2]

In light of the rapid rise of NHL incidence over two decades and the difficulties the scientific community has faced in attempting to explain this epidemic, it seems reasonable to carefully examine how these investigators went from association to causation.[3,4] More important is the question of whether such an inferential shift is scientifically justified. As Austin Bradford Hill emphasized in his now-classic article on causal inference, a key scientific concern in occupational epidemiology is distinguishing between association and causation.[5] Associations are numerical (statistical) features of data.[6] Causation, on the other hand, is a feature of the real world. Distinguishing between the two is, therefore, is a fundamental scientific concern with important implications for public health.

At least three possibilities could explain the shift from association to causation. First, new epidemiologic studies may have been published after the 2007 review. But, according to the authors of the 2008 meta-analysis, only one case-control study appeared in 2007 and it reported null results .[7] Thus, new studies of benzene and NHL cannot explain nor justify the causal claim found in the meta-analysis. A single null study simply cannot tip the scales in that way.

A second possibility is that the addition of a new member of the investigative team—Dr. Steinmaus—could have been responsible for the shift from association to causation. But this possibility can also be eliminated because personal subjective opinion and individual judgment do not matter more to inference-making than methodology.[8]

The third, and most likely, possibility to explain the shift to causation is methodological, specifically, the use of meta-analysis. The major difference between the 2007 publication—by Smith et al.—and the 2008 publication—by Steinmaus et al.—is the use of meta-analysis. Simply put, the investigators went from association to causation on the basis of a meta-analysis applied to essentially the same epidemiological evidence.

But can meta-analysis by itself generate a causal claim? That is the central methodological question here. And specifically, does the Steinmaus et al. meta-analysis of benzene and NHL provide sufficient rationale to move the scientific consensus on this controversial topic from association to causation?

In order to answer these questions, some historical and methodological background will be presented. Conclusions from other recent reviews and meta-analyses on the same topic will be reviewed along with

a systematic review of the extent to which causal claims emerge from meta-analysis in the broader practice of occupational epidemiology, as well as what the methodological literature says about the role of meta-analysis in causal inference.

My purpose here is not to perform a full causal analysis of the relationship between NHL and benzene, nor is it to re-analyze the studies. Rather, the purpose of this paper is to point out several cautionary (and critical) concerns about meta-analysis and causal inference in occupational epidemiology, using Steinmaus et al. as a case study.

Background: Prior Reviews and Meta-Analyses on Benzene and NHL

The conclusions found in the review by Smith et al. and in the meta-analysis by Steinmaus et al. do not exist in a scientific vacuum. At least 16 other reviews and 2 additional meta-analyses were published in the past ten years, from 1999 through 2008,[9-26] reflecting the intense interest in the benzene and NHL relationship as well as in the rapid rise in NHL incidence that remains largely unexplained.

The conclusions of these earlier evidentiary assessments are presented in Table I. It is fair to say that, prior to 2008, a broad consensus existed denying a causal link between benzene and NHL . Two recent reviews concluded that the evidence on causation was not sufficient.[19,24] For some reviewers, the direction of the relationship has not been established, putting at risk the notion that NHL and benzene are associated with one another, much less causally associated.[21,25] National Cancer Institute (NCI) investigators, in a well-respected textbook on cancer epidemiology published in 2006, devoted a single sentence to benzene in their chapter on NHL. They opined that benzene has not been shown to have a large role in lymphoma risk.[23] And, as noted earlier, the 2007 Smith et al. review concludes only that an association exists, a conclusion falling far short of causation. That leaves the Steinmaus et al. meta-analysis as the only reasonably systematic evidentiary assessment that attempts to move the scientific community from association to causation on the question of benzene and NHL. The two earlier meta-analyses, by Lamm et al. (2005)[20] and Wong and Raabe (2000),[10] concluded that workers were not at increased risk for NHL from benzene exposure.

It follows that the use of meta-analysis is the most likely source of the causal claim regarding benzene and NHL, rather than new scientific evidence or conclusions from earlier assessments. Indeed, Steinmaus et al. note that their primary purpose was to use meta-analysis to evaluate causal inference. A careful look at the role that meta-analysis plays in causal inference is, therefore, critically important.

Background: Meta-Analysis and Causal Inference

The primary role of meta-analysis in occupational epidemiology, indeed, in epidemiology in general, is not causal inference per se. The popular "Modern Epidemiology" methods text, for example, emphasizes that meta-analysis has two roles: (1) to summarize results (a synthetic goal) and (2) to estimate or identify differences among study-specific estimates of effect (an analytic goal).[27] Causal inference is another matter altogether. As Greenland notes, one should be aware of the limitations of meta-analysis; causal explanations are outside its realm.[27]

Causal inference is a much broader methodological concern, involving a systematic narrative review, an assessment of the extent to which the causal hypothesis of interest has been adequately tested, including but not limited to concerns about confounding and bias, as well as an assessment in terms of the full list of relevant causal criteria (or considerations): strength, consistency, dose-response, biological plausibility, specificity, temporality, experimental evidence, coherence, and analogy.[28]

Meta-analysis is not irrelevant to causal inference. It can increase the precision of estimates of effect and it provides an assessment of consistency but even there the meta-analyst must be very careful.[29] The synthetic (summarization) role of meta-analysis can give a false impression of consistency, especially if important differences in individual studies are not taken into account.[27]

Background: Causal Claims in Meta-Analyses of Occupational Epidemiology Studies

To what extent are causal claims made in the practice of meta-analysis? To answer this question, a search of PubMed was undertaken, using terms "meta-analysis, occupational" with limits set: title/abstract, published in the past 5 years. Sixty-two (62) English language publications met these requirements;[2,30-90] twenty (20) were eliminated because they summarized randomized clinical trials or intervention studies.[31,32,34,36,40,41,55,65,66,68,71,73,76,79,82,83,86-89] Of the remaining forty-two (42) meta-analyses, only six (6) mentioned causality in the abstract. Of these, only one—Steinmaus et al. (2008)—made a causal claim.[2] The remaining five (5) suggested that the evidence was insufficient to support causation or that causality remained unanswered.[35,53,61,62,90] It is important to point out that many—a large majority—of the meta-analyses revealed positive results, i.e. consistent and statistically significant increases in risk. But the most common (and appropriate) interpretation of these results was that the meta-analytical results revealed evidence of an association.

Can the Steinmaus et al. Meta-Analysis on Benzene and NHL Justify a Causal Claim?

Although meta-analysis has a role to play in causal inference, one should not use meta-analysis as the primary method for a causal evaluation. That is not its purpose. Even when a meta-analysis is of high quality, it provides, at best, an assessment of the consistency of results across studies and increased precision regarding the summary effect measure. If causal inference was the aim, then Steinmaus et al. should have at least discussed in detail the strength of the associations observed, dose-response patterns, specificity, and biological plausibility, to name only the most popular considerations used in the practice of causal inference in cancer epidemiology.[91]

Leaving aside these broader concerns, at least three issues specific to the Steinmaus et al. meta-analysis require careful consideration: first, the extent to which the studies on benzene and NHL were consistent (i.e. were not heterogeneous), second, correcting for the healthy worker effect (HWE), and third, the selective use of results from only "highly exposed" workers, obscuring dose-response patterns.

1. Heterogeneity and the Assessment of Consistency

Tests for heterogeneity in meta-analysis are used to determine whether the results are similar enough to be considered consistent (in a statistical sense).[92,93] Recently, a quantitative measure of

heterogeneity—I^2— was proposed; it measures the degree of inconsistency across studies in a meta-analysis.[94] The existence of significant heterogeneity calls for subgroup analysis of the studies. To put it another way, a statistically significant test for heterogeneity and a moderate to strong value of I^2 (i.e. a value greater than 45) means that the results are inconsistent. Combining results under those circumstances is not recommended.[27]

In the Steinmaus et al. meta-analysis, all of the studies of refinery workers and NHL were statistically heterogeneous (with p-values less than or equal to 0.01) and I^2 values ranging from 47 to 63. Clearly, these were inconsistent results. Combining them was not warranted. Heterogeneity was found for the cohort studies of refinery workers, the high exposure studies of refinery workers, and the same studies adjusted for the healthy worker effect. On the other hand, the case-control and cohort studies of "all studies" and "high-exposure studies" of NHL and benzene were, in general, not heterogeneous, a topic to which I will return.

2. Correcting for the Healthy Worker Effect

Traditionally, the healthy worker effect (HWE) is defined empirically: when worker mortality (or morbidity) rates are lower than those of an external comparison group, typically the general population.[95] Explanations for the HWE involve selection processes at time of hire and during employment. Differential information bias (e.g. cause-of-death) and workplace policies (e.g. smoking bans or disease screening programs) can also contribute to the observed effect. Two approaches for dealing with the HWE include: (1) using internal rather than external comparison groups and (2) quantitative correction algorithms.

Correcting for the HWE in the Steinmaus et al. meta-analysis, however, made no difference in the non-refinery studies of NHL and benzene. The cohort studies' uncorrected RR was 1.21; after the HWE correction, the RR 1.22. Together, the case-control and cohort studies' uncorrected RR was 1.22; after the HWE correction, the RR remained 1.22. For the "high exposure studies," the uncorrected RR was 1.49; after correction, the RR was 1.53. As noted above, the refinery studies were too heterogeneous to warrant being combined, although if the presence of heterogeneity is ignored, the correction for the HWE moved the RR in these studies from 1.21 to 1.42, a modest increase at best. A reasonable conclusion drawn from these analyses is not, as Steinmaus et al. claim, that the "HWE may mask important associations" between benzene and NHL. Rather, the more reasonable conclusion is that HWE correction had little or no impact on the evaluation of the link between benzene and NHL in these data .

3. A "High Exposure Sub-Group Only" Meta-Analysis and the Assessment of Dose-Response

A key consideration in causal inference is dose-response, not the precise calculation of a dose-response curve as done in the risk characterization step of risk assessment, but rather the general shape of the dose-response curve. If causal inference is the goal (as Steinmaus et al. assert), then it is important to carefully examine the extent to which the incidence (or mortality) of a disease increases as the exposure dose increases. Dose-response, in other words, involves the entire range of exposure estimates, including those workers with low exposures, modest exposures, and those with high exposures. In the

Steinmaus et al. meta-analysis, however, only high exposure sub-groups were analyzed. This carefully selected sub-group analysis produced relative risks (RRs) of 1.49 when dichotomous exposure studies were excluded, an increase from a RR of 1.22, when all studies were analyzed. When self-reported exposure studies were excluded, the RR rose to 2.12 from a selected group of six (out of 22) studies. The RRs of the moderately exposed and low exposure sub-groups were not reported. The shapes of the dose-response curve, therefore, were not taken into account.

The dose-response patterns for these 6 studies are shown in Table II.

These six "high-exposure no self-report" studies do not convincingly show a dose-response relationship for benzene and NHL. One is highly variable (Glass et al., 2003),[96] others are "U" shaped (Hayes et al., 1987; Collins et al., 2003),[97,98] one shows RR estimates less than one except at the highest exposure category (Bloemen et al., 2004),[99] and one is in the opposite direction from expectation (Schnatter et al., 1996).[100] From the fully transparent data, a reasonable conclusion is that there is no convincing dose-response relationship.

A related and equally troubling aspect of the Steinmaus et al. analysis was their decision to exclude the results of the Pliofilm cohort, the only worker cohort exposed to benzene and no other solvents.[102] They excluded the Pliofilm results because they felt that the study "had a very low cut-off point for defining exposed workers."[2] Inasmuch as the Pliofilm results were null (with an RR of 0.96), Steinmaus et al. might reasonably have surmised that the exclusion of this benzene-only exposed cohort would result in a higher risk estimate than what would have been found had these results been included. No sensitivity analysis was reported. As importantly, Steinmaus et al.'s protocol for including results in their "high exposure" analysis did not specify that studies whose cut-off points were "felt to be too low by the investigators" would be excluded. Or, to put it another way, there is reason to question the methodological integrity of the "high exposure sub-group" analysis on this point.

In the end, the strategy of including only "high exposure sub-groups minus the Pliofilm cohort results" produced modest RRs, only one indicating a doubling of the risk. As noted earlier, Steinmaus et al. did not discuss the relevance of the magnitude any risk estimate to causal inference. Yet it is well accepted that strength of association is a critically important causal concern, and uncontrolled confounding along with other biases can be responsible for modest RRs rather than the exposure of interest. Most importantly, examining the full range of dose-response values from these studies reveals that the patterns of dose-response relationships are highly variable. That Steinmaus et al. ignored these patterns further erodes their causal claim.

Discussion

Meta-analysis now holds a legitimate and increasingly popular place in the epidemiologist's toolbox of methods. Its methodological robustness does not extend, however, to causal inference. There, meta-analysis has a limited role to play. At its core, meta-analysis provides a way to average a group of numbers, numbers that happen to be the results of individual scientific studies, but numbers nevertheless. Meta-analysis also provides an assessment of the consistency of those numbers (relative to chance), a way to examine differences among different studies, and increases in precision of effect

measures. That is all that meta-analysis provides. It contributes to causal inference inasmuch as it provides a way to assess the consistency (and heterogeneity) of findings across studies, which is more than a simple calculation to be sure, but much less than a full account of the extent to which an exposure causes a disease.

With these methodological and inferential rules in hand, it is reasonable to assert that the Steinmaus et al. causal conclusion regarding benzene and NHL is not warranted. To say, as they did, that a meta-analysis provides new evidence that benzene causes NHL without a discussion of the limited role of meta-analysis in causal inference and without a full causal analysis is not any more justified than saying that benzene and NHL are associated without a definition for what constitutes an association (as Smith et al. did). Unsubstantiated claims about causation and association are equivalent to personal, subjective opinions. The science of occupational epidemiology is not well-served by this lack of methodological clarity and transparency.

Steinmaus et al. over-interpret the evidence regarding the refinery workers in their meta-analysis.[103] The refinery worker results are decidedly heterogeneous, which by definition, lack consistency. Inconsistent results cannot in this situation support the notion that benzene causes NHL.

And regardless of whether the HWE correction worked or not in the refinery worker study results, the same correction had no impact at all on the case-control and cohorts studies of benzene and NHL. Therefore, the Steinmaus et al. assertion that the HWE bias "could mask an important association" is like saying "maybe it does but probably it doesn't." No progress on that issue has been made.

That leaves only one, albeit important, concern: whether the Steinmaus et al. approach of limiting the analysis to "high exposure sub-groups only" provides evidence that "benzene exposure causes NHL." Steinmaus et al. would have us accept the notion that mixing highly exposed workers with moderately exposed and low-exposed workers is a form of non-differential misclassification bias. This sort of conceptual wordsmithing is unnecessary. Traditional epidemiological analysis encourages (if not requires) stratifying studies by exposure levels, especially if causal inference is the goal. It is certainly important to examine the risk of NHL in highly exposed workers but it is equally important to examine the risk of NHL in moderately exposed workers and those exposed to low levels, so that the full dose-response patterns can be assessed. Steinmaus et al. did not include this information in their paper. In sum, their assertion that causal inference rather than dose-response was their primary interest, runs counter to the well-accepted method of causal inference in occupational epidemiology.

It follows that Steinmaus et al. would have the scientific community forego not only the consistency of results but also dose-response patterns in causal inference. Their assessment of biological plausibility is equally troublesome. They provide a single unreferenced sentence: "other human, animal, and laboratory data linking benzene to NHL and immunotoxicity provide further support and biological plausibility to our findings." [2,p.377] This type of a bare-bones biological plausibility argument is insufficient.[104]

Regarding the strength of the reported associations, Steinmaus et al. do not examine the extent to which a RR of 1.22 (or, for that matter, 1.49) can be accepted as causal when other unmeasured

confounding factors are likely present. Nor do they discuss the causal significance of a single RR value of 2 found in the carefully selected subgroup analysis of "highly exposed worker studies not by self-report excluding the Pliofilm cohort." They argue that "while we cannot completely exclude the possibility that some other agent (e.g. other NHL risk factor) is causing the effects we identified, most evidence suggests the major causative agent is benzene." [2,p. 376] The obvious problem here is that these "other agents" could easily explain these modest (weak) associations. In the end, strength of association appears not to be an important consideration in the Steinmaus et al. view of causal inference. All that appears to be required is a statistically significant elevated risk, whatever the magnitude.

Having reduced causal analysis to something that does not require consistency, dose-response, biological plausibility, or strength, Steinmaus et al. leave us wondering what else remains to justify a causal claim in occupational epidemiology.

If Hill's criteria (or considerations) are a guide—and that seems reasonable inasmuch as institutions such as the Environmental Protection Agency (EPA),[105] the International Agency for Research on Cancer (IARC),[106] and the Institute of Medicine (IOM)[107] use them as do most professional practitioners—then the remaining considerations are specificity, experimentation, coherence, temporality, and analogy. None of these criteria are mentioned much less discussed by Steinmaus et al. And we can reasonably assert that specificity is a problem here for all the studies of benzene and NHL except for the Pliofilm cohort whose results were excluded from the analyses. There are potentially many factors that could cause NHL. Experimentation is not relevant here and temporality is satisfied. Coherence and analogy are probably more important than most practitioners recognize even in this situation, but that topic is beyond the scope of this commentary. The important observation is that Steinmaus et al. make a causal claim regarding benzene exposure and NHL using only statistical significance—the magnitude of the elevated relative risk being irrelevant— and an unsubstantiated mention of biological plausibility.

Conclusion

Examining the role of meta-analysis in making causal claims is important because meta-analysis has emerged as a legitimate and widely-used methodology in occupational epidemiology. Using meta-analysis alone, however, to generate causal claims is not appropriate. As illustrated here, this critical analysis revealed that Steinmaus et al. used meta-analysis to make a claim about benzene and NHL from the same scientific evidence that many others determined falls short of causality. That consensus remains intact.

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Table I
Conclusions of Reviews and Meta-Analyses
Regarding the Relationship between NHL and Benzene
1999-2008

(Steinmaus et al., 2008)

"(Our analysis) provides new evidence that benzene causes NHL." (p. 374)

"In conclusion, the results of these analyses suggest that benzene causes NHL..." (p. 377)

(Rodriguez-Abreu et al., 2007)

No mention of benzene. However: "Occupational exposure to solvents has...been associated with an increased risk."(p. i8)

(Smith et al., 2007)

"We conclude that, overall, the evidence supports an association between occupational benzene exposure and NHL." (p. 385)

(Alexander et al., 2006)

"...there is no epidemiologic evidence supporting a causal relationship between working in the petroleum industry and risk of developing NHL." (p.12)

(Ekstrom-Smedby, 2006)

"Benzene is a well-known leukemogenic agent (primarily causing acute myeloid leukemia), but current evidence for a causal link with NHL...is insufficient."(p. 264)

(Hartge et al., 2006)

"Benzene exposure, a clear risk factor for leukemia, has not been shown to play a large role in lymphoma risk." (p. 908)

(Mehlman, 2006)

"A large number of studies have shown statistically significant increased risk for NHL in persons exposed to benzene." (p.120) "The generally accepted standard of scientific probability of data showing a p value of 0.05 or less is generally accepted as demonstrating a likelihood of 95% that the association is not due to chance. Thus...(it is) reasonable to conclude that exposure to benzene or to solvents or to products containing benzene is causally related to NHL." (p. 127)

(Grulich et al., 2005)

"There is an extensive literature on the relationship between occupational exposure to solvents and NHL, but there is no consensus on the direction of the relationship.

(Lamm et al., 2005)

"In toto, the studies do not demonstrate an increased risk of NHL from benzene exposure." (p. 234)

(Muller et al., 2005)

"Various environmental exposures have also been examined, including benzene...These have all demonstrated no definite relation to NHL." (p. 8)

(Wong and Fu, 2005)

"...there is little epidemiologic evidence supporting an association between benzene exposure and NHL." (p. 40)

(Fisher and Fisher, 2004).

"...studies of specific occupations and specific chemicals have suggested some increase in the risk of NHL among exposed persons; however, exposure assessment is quite difficult due to changing patterns over time. These problems of exposure measurement/classification have limited the conclusion that can be drawn from these studies." (p. 6531)

(Pyatt, 2004)

"Despite considerable speculation and opinions that have appeared in the literature, however, the available data supporting a link between benzene exposure and NHL are equivocal at best." (p. 544)

(Smith et al., 2004)

"There are a number of potential causal models in which occupational...chemical exposures are implicated (in the etiology of NHL)...including a range of solvents. However, using these as causal models in molecular epidemiology is difficult because...the association with NHL is not established." (p. 385)

(Chiu and Weisenburger, 2003)

"The increasing incidence of NHL is poorly understood. Increase in NHL may be attributed to immunodeficiency, various infections, familial aggregation, blood transfusion, genetic susceptibility, diet, and chemical exposures to pesticides and solvents." (p. 161)

(Swerdlow, 2003)

"...there are not any established occupational causes of (NHL)." (p. S9)

(Hayes et al., 2001)

"Limited data suggest that lymphomas might be associated with benzene exposure." (p. 120)

(Baris and Zahm, 2000)

"The etiologic agents responsible for excess risks (of NHL in rubber workers, petroleum refinery workers, vinyl chloride workers, chemists, dry cleaners, and aircraft maintenance workers) have not been identified definitively, but the occupations have in common exposure to organic solvents." (p. 388-389)

(Wong and Raabe, 2000)

"...employees in the petroleum industry, who are exposed to benzene or benzene-containing products, are not at increased risk for NHL." (p. 565)

(O'Connor et al., 1999)

"...there is compelling evidence to suggest a role for several atmospheric pollutants, the most important of which is benzene in the genesis of NHL. The rise in environmental levels of benzene and related toxic compounds produced by increased numbers of motor vehicles has closely paralleled the marked increase of disease since World War II." (p. 452)

Table II

Dose-Response Relationships in Six Benzene-NHL Studies

Values in red are those used by Steinmaus et al. in a "high-exposure subgroup only" meta-analysis

Glass et al. (2003)	
Less than 1 ppm-years	1.00
1-2 ppm years	0.90
2-4 ppm years	0.56
4-8 ppm years	1.37
8-16 ppm years	0.95
Greater than 16 ppm-years	1.48
Schnatter et al. (1996)	
0.0-0.01 mean ppm	1.00
0.01-0.19 mean ppm	1.87 (0.13-26.9)
0.20-0.49 mean ppm	0.93 (0.08-7.19)
0.50-6.16 mean ppm	0.00 (0.0-10.7)
Bloemen et al. (2004)	
Less than 5 years duration	0.87 (0.32-1.88)
5-9 years duration	0.92 (0.02-5.11)
Greater than 10 years duration	2.15 (0.44-6.28)
Collins et al. (2003)	
None	1.4 (0.9-2.2)
Less than 7	1.3 (0.0-7.4)
7-40	0.7 (0.0-4.2)
Greater than 40	1.8 (0.4-5.1)
Hayes et al. (1987)	
Less than 10 average ppm	2.7 (0.7-10.6)
10-24 average ppm	1.7 (0.3-10.2)
Greater than 25 average ppm	4.7 (1.2-18.1)
Wong (1987)	
Non-exposed	1.00
Less than 180 ppm-months	1.40
180-719 ppm-months	2.23
Greater than 720 ppm-months	1.07