CONTROLLED EXPOSURE TO FORMALDEHYDE VIA INHALATION:

A Categorical Regression Analysis of Human Exposure and Response

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Abstract

Human experimental data provide a robust scientific basis for deriving human health effects criteria. However, adequate human chronic or acute exposure data are rarely available. In the absence of such data, compensatory procedures involving the extrapolation of laboratory animal data, combined with modifying and uncertainty factors, are used.

Volunteers acutely exposed to formaldehyde, an irritant, via inhalation were collected, reviewed and assessed. These data include a number of experiments conducted under controlled exposure conditions of concentration (C) and time (t). For these studies, various health-related endpoints were characterized with respect to the level of severity observed. Data from controlled exposure studies such as these are amenable to analysis by categorical regression where severity levels are represented as categories. Analyzed in this manner, the two primary exposure parameters (C and t) can be related to exposure-effect severity to derive human health effects criteria. An important advantage of this approach is that all relevant data can be used in the derivation as opposed to a NOAEL for the critical effect. The benefit of doing so allows health risks to be estimated across various exposure levels.

The U.S. EPA's CatReg Program utilizes categorical regression to establish the relationship between C-t and severity of the resulting effect. Response variability and uncertainty are addressed by confidence limits bounding the derived relationship curves. Three statistical models (Logit, Probit and Complementary Log-Log) are available in the CatReg Program. Preliminary analysis indicates that depending on how the data are categorized, the complementary log-log model (with untransformed base 10 levels of C and t) and the probit model (with logarithms of C and t) yielded the minimum deviance of these three models for the acute exposure formaldehyde data. These data comprise 250 observations from six studies originally categorized by four severity levels, and then collapsed into three (no/mild, moderate, severe effects).

INTRODUCTION

Toxicity data may be analyzed by categorical regression after effects have been assigned to ordinal severity categories (e.g., no effect, adverse effect, severe effect) and associated with up to two independent variables corresponding to the exposure conditions (e.g., concentration and duration) under which the effects occurred. A US Environmental Protection Agency (US EPA) model, CatReg, calculates the probabilities of the different severity categories over the continuum of the variables describing exposure conditions. (Strickland, 2000) The advantage of such an approach in deriving exposure criteria compared to those based on a single data point has been described by the US EPA:

> "A major criticism of the NOAEL/LOAEL paradigm is that its reliance on a single data point as the basis of the derivation does not allow for specific consideration of the shape of the dose-response curve, the number of animals in the group, or the statistical variation in the response and its measurement…The methods making use of mathematical dose-response models, Benchmark Concentration and categorical regression (as opposed to NOAEL method), are preferred when the toxicological data are sufficient to support these methods…because they use information from the entire dose-response curve rather than from a single experimental point (US EPA 1998)"

and subsequently by the US EPA Science Advisory Board:

> "The [categorical regression] process makes use of every bit of data available…The underlying premise of the approach is that the severity of the effect, not the specific measurement or outcome incidence, is the information needed for assessing exposure-response relationships for non-cancer endpoints….All the available data are graphed on a single chart and one can immediately get a rough picture of the level of the concentration multiplied by time values that can be expected to cause adverse effects of varying severity." (USEPA SAB 1998)

This report is the fourth compound in a series of studies using categorical regression to analyze human experimental data. Earlier reports on HD (sulfur mustard) and nerve agent VX have not been published; the third report on GB (Sarin) is in preparation (Kelly 2005).

For this report, a thorough literature review of human formaldehyde-exposure studies was conducted (see reference section). On the basis of adequate documentation of time, concentration and eye irritation effect, six of the 15 reviewed studies were deemed suitable for CatReg analysis (Andersen 1979, Green 1987, Kulle 1993, Schachter 1986, Schachter 1987, Witek 1987).

The effects of each exposure were noted and ranked according to the following classification, which represented subjective reporting of eye irritation supplemented by additional investigator observations of respiratory effects.

The observed exposure effects were categorized as follows:

0= No effect noted or reported.

1= Mild signs and symptoms; irritation was noticed but not considered annoying; some dryness in nose and throat; no bronchoconstriction.

2= Moderate signs and symptoms; irritation was annoying; no bronchoconstriction.

3= Severe signs and symptoms; incapacitating.

SUMMARY OF FORMALDEHYDE EXPERIMENTAL DATA IN HUMANS USED IN STATISTICAL ANALYSIS

To be included in this study, the supporting data must be:

- Unclassified and publicly available
- Controlled exposures only; no case reports or non-quantified observations
- Acute exposures only; no extrapolation from chronic exposures
- Well-characterized concentration (C) and duration (t) of exposure
- Thorough characterization of severity of observed health endpoints, allowing categorization of effects

These studies were then evaluated to identify the key health endpoint of interest, ideally the most common adverse effect of concern if enough supporting data are available for evaluation. For formaldehyde, the most common effect is subjective irritation. The range of irritation response was then categorized by severity, and categorical regression used to analyze results by time, concentration and severity.

This section summarizes the key results of the six studies used in the CatReg analysis. The original studies should be consulted for complete details.

Andersen 1979: Sixteen young, healthy subjects were exposed to each of 0.3, 0.5, 1.0 or 2.0 mg formaldehyde per m^3 (subsequently recoded to 0.24, 0.41, 0.82, or 1.63 ppm), in random order of exposure, over a period of five hours. Exposure occurred under controlled conditions, for seven to eight hours a day, for four consecutive days. Eye irritation and other subjective symptoms were recorded.

Green 1987: 22 healthy, non-smoking subjects were exposed to 3 ppm formaldehyde for one hour under controlled conditions while exercising heavily and intermittently. 16 asthmatic subjects were similarly exposed while performing moderate exercise intermittently. Symptoms and alterations in pulmonary function were recorded. All subjects reported consistent irritant symptoms.

Kulle 1993: This reanalysis of the data originally reported in Kulle 1987 involved randomly exposing 19 subjects to 0, 0.5, 1.0, 2.0, or 3.0 ppm formaldehyde while either

resting or exercising. Significant dose-response relationships in eye irritation were observed.

Schachter 1986: 15 healthy, nonsmoking subjects were randomly exposed to 2 ppm formaldehyde for 40 minutes under controlled conditions. The same exposures were repeated on a separate day with the subjects performing moderate exercise for 10 minutes. Eye irritation was highest upon initial exposure and decreased over 30 minutes. Exercising did not exacerbate reported symptoms.

Schachter 1987: 15 laboratory workers, who were routinely occupationally exposed to formaldehyde, were exposed to 2 ppm formaldehyde for 40 minutes under controlled conditions. These exposures were repeated on two more occasions including 10 minutes of exercising. Symptoms were mild and transient, with unusual odor and eye irritation the most frequent complaint.

Witek 1987: 15 asthmatic volunteers were exposed to 2 ppm formaldehyde for 40 minutes under controlled conditions. These exposures were repeated on a separate day including 10 minutes of moderate exercise. Complaints included mild or moderate eye, nose and throat irritation.

METHODS OF STATISTICAL ANALYSIS

Model

The U.S. EPA's CatReg Program (Strickland, 2000) utilizes categorical regression to establish the relationship between concentration (C), time, and severity of the resulting effect. Response variability and uncertainty are addressed by confidence limits bounding the derived relationship curves. Three statistical models (Logit, Probit and Complementary Log-Log) are available in the CatReg program.

Data

The data comprise 250 observations from six studies investigating the effect of formaldehyde on eye irritation. Four severity levels are coded as s=0, 1, 2, 3, as described above (no effect, mild, moderate, severe).

Two censored regimes were defined for the Green study. In this report information was only available on whether subjects were classified in either the none/mild or the moderate/severe categories. Therefore for the Green study, SevLo and SevHi were coded either 0-1 or 2-3, respectively.

Number of observations by severity level

Severity Level	Observations	Comments
0	105	
1	110	81 observed and 29 censored
2	20	
3	15	6 observed and 9 censored

Conditioning variables are formaldehyde concentration in parts per million[1], duration of exposure in hours, a binary variable Activity that denotes whether the subject exercised (E) at any time during exposure or rested (R), and a binary variable Status that denotes whether the subject was healthy (H) or asthmatic (A).

Statistical Model

The quantal response data obtained from human exposure to formaldehyde were analyzed using ordered categorical statistical methods. The response variable was coded to reflect the treatment effect. The estimated probability of a severity level or a more extreme severity level was related to the concentration of the chemical, C, and duration of exposure to the chemical, T. Let s denote the response category such that s=0 represents the lowest effect and increasing integer values of s reflect progressively more severe effects, then the statistical model can be written as

$$P(Y \geq s \mid C, T) = F_s[C, T \mid \theta]$$

where F[·] denotes a cumulative distribution function and θ represents an unknown vector of parameters. Obviously $P(Y \geq 0)=1$.

The unknown parameters were estimated using the method of maximum likelihood by maximizing the log likelihood over the sample of 250 observations. For the present case where max(s)=3, the i^{th} observation of the log likelihood has the form

$$\ell_i = I_{\{y_i=0\}} \ln(1-F_1) + I_{\{y_i=1\}} \ln(F_1 - F_2) + I_{\{y_i=2\}} \ln(F_2 - F_3) + I_{\{y_i=3\}} \ln(F_3) + I_{\{0 \leq y_i \leq 1\}} \ln(1-F_2) + I_{\{2 \leq y_i \leq 3\}} \ln(F_2)$$

where $I_{\{\cdot\}}$ is the indicator function and the last two terms in the log likelihood pertain to the two censored regimes which arise from the Green study.

Statistical Specification

Choice of the distribution function, F[.], and the proper transformation of C and T are largely empirical issues. Using CatReg, the deviance statistics were calculated for

[1] CatReg will label this as mg/m3, but the graphics have been edited to show ppm.

combinations of distribution functions and linear and logarithmic (base 10) transformations of the factors.

	Deviance Statistics under Various Specifications	
Link Function	Linear Factors	Log Factors
Logit	448.280	451.398
Probit	451.316	452.436
Complementary Log-Log	443.056	449.213

Because degrees of freedom are identical (df=245) in each of the estimated models, model selection can be based on the specification that minimizes the deviance statistic. Although there are minor practical differences in the fits of the various models, the ordered complementary log-log model with untransformed base 10 levels of C and t is chosen. The complementary log-log link assumes a Gumbel (extreme value) distribution which is asymmetric unlike the logistic and normal distributions associated with the other link functions considered above.

CatReg Estimation Results

```
Input file   : fappm.csv
Filtered data: none
Model        : cumulative odds model
Link         : cloglog
Clustering   : none
Deviance     : 443.0561

Scale:
     Concentration: mg/m3
     Duration     : Hours

Stratification:
     Intercept    :
     Concentration:
     Duration     :

Coefficients:
       Estimate   Std. Error   Z-Test=0     p-value
SEV1  -2.9036968  0.4427337   -6.558563      1e-05
SEV2  -4.8134301  0.5311424   -9.062409      1e-05
SEV3  -6.3540554  0.6449477   -9.852048      1e-05
CONC   1.1142211  0.1754131    6.351982      1e-05
TIME   0.3261790  0.0705682    4.622180      1e-05
```

Gauss Estimation Results

```
     Log likelihood value at convergence    : -221.528051
     Deviance statistic                     :  443.056102
     Number of observations                 :       250.0
```

	Estimate	StdErr(H)	Asymptotic t-value(H)	p-value(H)	StdErr(S)	p-value(S)
SEV1	-2.90370	0.44273	-6.55856	0.00000	0.40926	0.00000
SEV2	-4.81343	0.53114	-9.06241	0.00000	0.51358	0.00000
SEV3	-6.35406	0.64495	-9.85204	0.00000	0.68641	0.00000
CONC	1.11422	0.17541	6.35198	0.00000	0.14976	0.00000
TIME	0.27144	0.06335	4.28500	0.00002	0.05893	0.00000

Model Assessment and Comparison of Estimators

Both statistical packages methods show remarkable agreement. Calculated values agree to at least five significant digits. Although not available in CatReg, the GAUSS output provides standard errors based on the sandwich estimator (denoted by S) of the parameter variance-covariance matrix. Under the assumptions of independence and proper specification of the conditional mean function, these standard errors are robust to distributional misspecification (White, 1982). Common causes of distributional misspecification are incorrect choice of the distribution function or non-constant variances. In the present case, however, standard errors under both methods are fairly similar.

The deviance statistic suggests that model fit is inadequate given that an implicit test of the hypothesis that the 245 over-identifying restrictions are consistent with the data generating mechanism yields a test statistic of 443.06 (p=0.000). This result is not particularly surprising in view of the substantial "noise" in the data. This noise is a result of the differing inter-individual responses and subjects' assessments of eye irritation when exposed to FA. There are several avenues for addressing this misspecification such as: i) incorporating additional explanatory variables; ii) estimating an unrestricted model; and iii) combining severity levels. We will consider each of these approaches in turn.

Stratification

The effects of potentially important qualitative explanatory variables can be assessed in CatReg by stratifying parameters according to the levels of these variables. In the case of the Activity variable, we stratify the intercept and both the concentration and duration coefficients. CatReg results are

```
Input file   : fappm.csv
Model        : cumulative odds model
Link         : cloglog
Deviance     : 436.5538

Scale:
     Concentration: mg/m3
     Duration     : Hours

Stratification:
     Intercept    : Activity
```

```
     Concentration: Activity
     Duration     : Activity

Coefficients:
              Estimate  Std. Error   Z-Test=0     p-value
SEV1        -3.1206077  1.05799032  -2.9495616    0.00318
SEV2        -5.0767275  1.15717112  -4.3871882    0.00001
SEV3        -6.6337063  1.20797027  -5.4916139    0.00001
E:INTERCEPT  0.0000000  0.00000000         NA         NA
R:INTERCEPT  0.1505121  1.11426280   0.1350777    0.89255
E:CONC       1.2047545  0.44573244   2.7028647    0.00687
R:CONC       1.2818950  0.19692973   6.5094032    0.00001
E:TIME       0.1682231  0.16596923   1.0135798    0.31078
R:TIME       0.3218316  0.07926736   4.0600776    0.00005
```

An additional three coefficients are estimated—an intercept term for those in the Resting group and separate coefficients on concentration and time for the Exercising and Resting groups. A likelihood ratio test of the hypothesis that stratification by Activity is uninformative yields a test statistic of 6.50 (p=0.090).

In the case of the health Status variable, stratified coefficients can not be estimated for the intercept and both the concentration and time variables due to a lack of variation in observed levels of concentration for those with asthma. So only a stratified intercept and time coefficient are estimated:

```
Input file   : fappm.csv
Model        : cumulative odds model
Link         : cloglog
Deviance     : 441.2019

Scale:
     Concentration: mg/m3
     Duration     : Hours

Stratification:
     Intercept    : Status
     Concentration:
     Duration     : Status

Coefficients:
              Estimate  Std. Error   Z-Test=0     p-value
SEV1        -1.8361247  0.94595024  -1.9410373    0.05225
SEV2        -3.7093771  1.01516951  -3.6539485    0.00026
SEV3        -5.2558870  1.07527714  -4.8879370    0.00001
A:INTERCEPT  0.0000000  0.00000000         NA         NA
H:INTERCEPT -1.2851046  0.97666008  -1.3158156    0.18824
CONC         1.1679173  0.18062408   6.4660111    0.00001
A:TIME      -1.4905981  1.60058458  -0.9312835    0.35171
H:TIME       0.3607361  0.07774378   4.6400645    0.00001
```

A likelihood ratio test of the hypotheses that the stratified intercept is zero and the stratified coefficients on time are equal yields a test statistic of 1.854 (p=0.396).

Therefore we conclude that neither Activity nor health Status significantly contributes to explaining the categorical regression.

Unrestricted Categorical Regression

Another test of specification that is commonly performed is that of the constant coefficients on the treatment effects across severity levels—the parallelism assumption. CatReg results are:

```
Input file   : fappm.csv
Model        : unrestricted cumulative model
Link         : cloglog
Deviance     : 418.3831

Scale:
     Concentration: mg/m3
     Duration     : Hours

Coefficients:
            Estimate   Std. Error    Z-Test=0     p-value
SEV1       -3.3319370  0.53525705  -6.22492879    0.00001
SEV2       -3.4951314  0.79679722  -4.38647536    0.00001
SEV3       -2.2856184 12.01428272  -0.19024177    0.84912
CONC:SEV1   1.2466081  0.22636827   5.50699121    0.00001
TIME:SEV1   0.4171933  0.08101284   5.14971792    0.00001
CONC:SEV2   0.8908328  0.29025819   3.06910468    0.00215
TIME:SEV2  -0.1346707  0.14758221  -0.91251276    0.36150
CONC:SEV3   0.2262602  6.00376513   0.03768638    0.96994
TIME:SEV3  -1.7841887  1.63116889  -1.09380991    0.27404
```

A likelihood ratio test of the restricted versus the unrestricted model yields a test statistic of 24.67 (p=0.000) that suggests that the unrestricted model better fits the data. Examination of the unrestricted model turns up some conflicting results in that the time coefficient is negative for severity levels two and three. Also the severity level three concentration parameter possesses a coefficient that is substantially smaller than for the other two levels, but the aforementioned coefficients all have standard errors that are relatively large. This leads to considering a restricted model specified such that $\beta_{C1}=\beta_{C2}=\beta_{C3}$ and $\beta_{T2}=\beta_{T3}=0$, that is that concentration has the same coefficient across severity levels and time has a zero coefficient for severity levels two and three. Unfortunately, CatReg cannot estimate this model. The GAUSS results are:

```
Log likelihood value at convergence    :    -212.867
Deviance statistic                     :     425.734
Number of observations                 :         250
```

	Estimate	StdErr(H)	Asymptotic t-value(H)	p-value(H)	StdErr(S)	p-value(S)
SEV1	-3.18479	0.43401	-7.33810	0.00000	0.37425	0.00000
SEV2	-4.29379	0.44536	-9.64120	0.00000	0.38606	0.00000
SEV3	-5.82907	0.57219	-10.18734	0.00000	0.54493	0.00000
CONC	1.14811	0.17033	6.74055	0.00000	0.14012	0.00000
$TIME_{SEV1}$	0.40981	0.07131	5.74678	0.00000	0.06645	0.00000
$TIME_{SEV2}$	0					
$TIME_{SEV3}$	0					

A likelihood ratio test of the restrictions implied by this model (versus the unrestricted cumulative model) yields a test statistic of 7.351 (p=0.118). Interestingly, this model estimates the same number of parameters as the original model that has a deviance of 443.056. This model has a smaller deviance because it does not restrict the coefficients on time to be identical across severity levels. Nevertheless, neither this model nor the unrestricted cumulative model passes the general specification test because their associated deviances are too large by a factor of almost two.

Combining Severity Levels

A concern when reviewing the clinical trials that form our dataset is that subjects may not be capable of distinguishing mild eye irritation relative to background sensation. If that is the case, then we should investigate re-categorizing the data into three severity levels such that s=0 represents negligible eye irritation (i.e., no or mild effects), s=1 represents moderate eye irritation and s=2 represents severe eye irritation. CatReg has the capability of recoding a dataset using the "join" command.

Data and Statistical Model

By combining severity categories zero and one, the data now are distributed as follows.

Number of observations by severity level

Severity Level	Observations	Comments
0 (none/mild)	215	
1 (moderate)	20	
2 (severe)	15	6 observed and 9 censored

Now we have max(s)=2, so the i^{th} observation of the log likelihood has the form

$$\ell_i = I_{\{y_i=0\}} \ln(1-F_1) + I_{\{y_i=1\}} \ln(F_1 - F_2) + I_{\{y_i=2\}} \ln(F_2) + I_{\{1\le y_i\le 2\}} \ln(F_1)$$

where $I_{\{.\}}$ is the indicator function and the last term in the log likelihood pertains to the remaining censored regime which arises from the Green study.

Statistical Specification

Deviance Statistics under Various Specifications

Link Function	Linear Factors	Log Factors
Logit	206.442	204.465
Probit	204.916	203.701
Complementary Log-Log	207.043	204.747

By adopting the criterion of minimizing the deviance statistic, we now choose the probit link function and perform a logarithmic transformation of the factors. This statistical specification will be used in all subsequent analysis.

CatReg Three Severity Level Model

```
Input file   : fa2ppm.csv
Model        : cumulative odds model
Link         : probit
Deviance     : 203.7010

Scale:
     Concentration: log10( mg/m3 )
     Duration     : log10( Hours )

Stratification:
     Intercept    :
     Concentration:
     Duration     :

Coefficients:
           Estimate   Std. Error   Z-Test=0    p-value
SEV1      -1.7133822  0.2925348   -5.857021    0.00001
SEV2      -2.5298901  0.3231633   -7.828518    0.00001
LG10CONC   2.4681248  0.8192843    3.012538    0.00259
LG10TIME  -0.3605163  0.3426878   -1.052026    0.29279
```

GAUSS Results

```
     Log likelihood value at convergence    : -101.850517
     Deviance statistic                     :  203.701033
     Number of observations                 :       250.0

     Estimate    StdErr(H)  Asymptotic  p-value(H) StdErr(S) p-value(S)
                            t-value(H)

SEV1   -1.71338    0.29253   -5.85702    0.00000    0.25827    0.00000
SEV2   -2.52989    0.32316   -7.82852    0.00000    0.31651    0.00000
LGCONC  2.46812    0.81928    3.01254    0.00259    0.70926    0.00050
LGTIME -0.36052    0.34269   -1.05203    0.29279    0.31250    0.24864
```

A two-sided z-test that the coefficient on time equals zero would not be rejected at the 0.10 level of significance using the standard errors calculated either from the Hessian or from the robust estimator of the parameter variance-covariance matrix. The interpretation of the negative coefficient on time is that longer exposures tend to reduce reported severity when concentrations are held constant.

The general test of model specification based on the deviance statistic (i.e., a test that the 246 over-identifying restrictions are consistent with the data generating mechanism) yields a statistic of 203.70 (p=0.977). This implies that the estimated model fits the data well. The fact that the robust standard errors are uniformly smaller than those from the estimated Hessian implies that the data may be under-dispersed or the underlying distribution thinner tailed relative to that admitted by the statistical model.

Before estimating the model without the log of time factor, we consider several generalizations. In each case a likelihood ratio test of the restrictions implied by the more parsimonious model relative to the generalization was calculated and is presented in the table below. The intercept and coefficients on both the factors were stratified by Activity. Under stratification by Status, only the intercept and log time were stratified due to the lack of variation in concentration as mentioned previously. Recall that the unrestricted model allows differing coefficients on the factors across severity levels. The quadratic in log time model was estimated in order to evaluate whether a temporal response pattern that rises then falls could be identified.

Model	Test Statistic	Degrees of Freedom	p-value
Stratify by Activity	3.895	3	0.273
Stratify by Status	1.423	2	0.491
Unrestricted	5.070	2	0.079
Quadratic in Log Time	0.161	1	0.688

Based on these results, we adopt the restricted model in which the time factor has been omitted.

CatReg Results

```
Input file   : fa2rppm.csv
Model        : cumulative odds model
Link         : probit
Deviance     : 204.8274

Scale:
     Concentration: log10( mg/m3 )

Coefficients:
           Estimate  Std. Error   Z-Test=0     p-value
SEV1      -1.808278   0.2688628   -6.725653    0.00001
SEV2      -2.614100   0.3044426   -8.586512    0.00001
LG10CONC   2.717370   0.7575276    3.587156    0.00033
```

The corresponding GAUSS results are:

```
     Log likelihood value at convergence    : -102.413693
     Deviance statistic                     :  204.827387
     Number of observations                 :       250.0

      Estimate    StdErr(H)  Asymptotic  p-value(H) StdErr(S) p-value(S)
                             t-value(H)

SEV1   -1.80828    0.26886   -6.72566    0.00000    0.21490    0.00000
SEV2   -2.61410    0.30444   -8.58652    0.00000    0.27094    0.00000
LGCONC  2.71737    0.75753    3.58716    0.00033    0.59404    0.00000
```

Again we see that the robust sandwich errors are smaller than those derived from the Hessian matrix. Of particular interest is whether confidence intervals for the EC_{10} levels of formaldehyde should be calculated using the robust parameter variance-covariance matrix. This issue can be addressed by comparing three sets of confidence intervals for EC_{10}: i) the default confidence intervals from CatReg which are constructed using the delta method; ii) robust confidence intervals constructed using the delta method; and iii) bootstrap confidence intervals based on sampling from the data and re-estimating the model 400 times.

Effective Concentration Levels—EC_{10}

A primary advantage to using the ordered categorical response model in the analysis of toxicant exposure is the capability to calculate the probabilities of severity of response based on exposure concentrations and durations. EC_{10} denotes the effective exposure concentration, given a severity level and exposure time, which is associated with a physiological effect in an estimated 10 percent of subjects. Since EC_{10} is a function of estimated model parameters, CatReg uses the delta method to obtain a corresponding standard error. Under the assumption that EC_{10} is normally distributed, a 95% confidence interval can then be constructed by adding to and subtracting from EC_{10} 1.96 times the standard error. When base 10 logarithms are used to transform C and T, the corresponding base 10 levels of C and its 95% confidence interval are typically obtained by exponentiating.

An alternative approach is to employ the bootstrap. For each bootstrap sample, EC_{10} is calculated. Then the mean EC_{10} level, its standard deviation, and an empirical 95% confidence interval can be obtained from the bootstrap replications. If the model is estimated using the base 10 logs of C and T, then the corresponding base 10 quantities are found using the exponentiated value of EC_{10} from each bootstrap replication.

The following tables present the EC_{10} estimates for severity levels one and two using the CatReg computations and also using 200 bootstrap replications estimated with GAUSS.

Severity Level 1 (Moderate Effects)

Method	Log_{10}Concentration	Standard Error
CatReg Delta	0.19384	0.05381
Robust Delta	0.19384	0.04714
$Bootstrap_{400}$	0.19376	0.04944

Method	Effective Concentration (ppm)	95% Confidence Interval (ppm)
CatReg Delta	1.5625	1.2257—1.9921
Robust Delta	1.5625	1.2631—1.9330
$Bootstrap_{400}$	1.5724	1.2488—1.9343

Severity Level 2 (Severe Effects)

Method	Log_{10}Concentration	Standard Error
CatReg Delta	0.49038	0.08131
Robust Delta	0.49038	0.07584
$Bootstrap_{400}$	0.50012	0.08685

Method	Effective Concentration (ppm)	95% Confidence Interval (ppm)
CatReg Delta	3.0930	2.1430—4.4643
Robust Delta	3.0930	2.1965—4.3555
$Bootstrap_{400}$	3.2317	2.3386—4.9601

Here we see that the confidence intervals calculated using the robust standard errors are the narrowest. The mean effective concentration is greater under the bootstrap estimator. Further the confidence intervals for the EC_{10} base 10 concentrations of formaldehyde are the most liberal from the bootstrap estimator. Note that these are empirical confidence intervals obtained from ordering the exponentiated EC_{10} levels and taking the upper and lower 2.5 percentiles. The fact that the CatReg confidence intervals for the EC_{10} base 10 concentrations of formaldehyde are generally bounded by the other two methods is a reasonable compromise.

Figure 1. Probability Plot for Severity Level 1 (Moderate Effects)

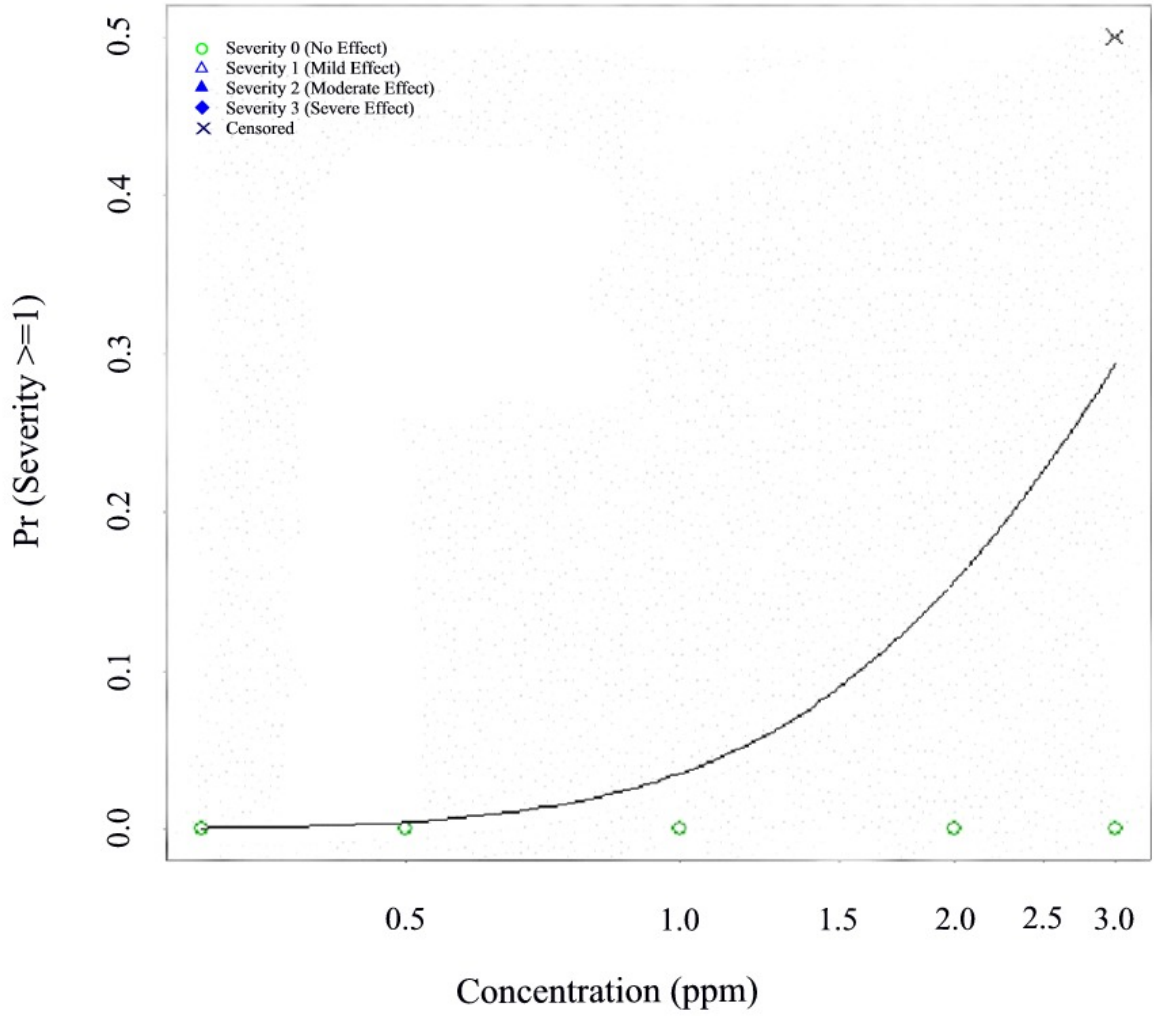
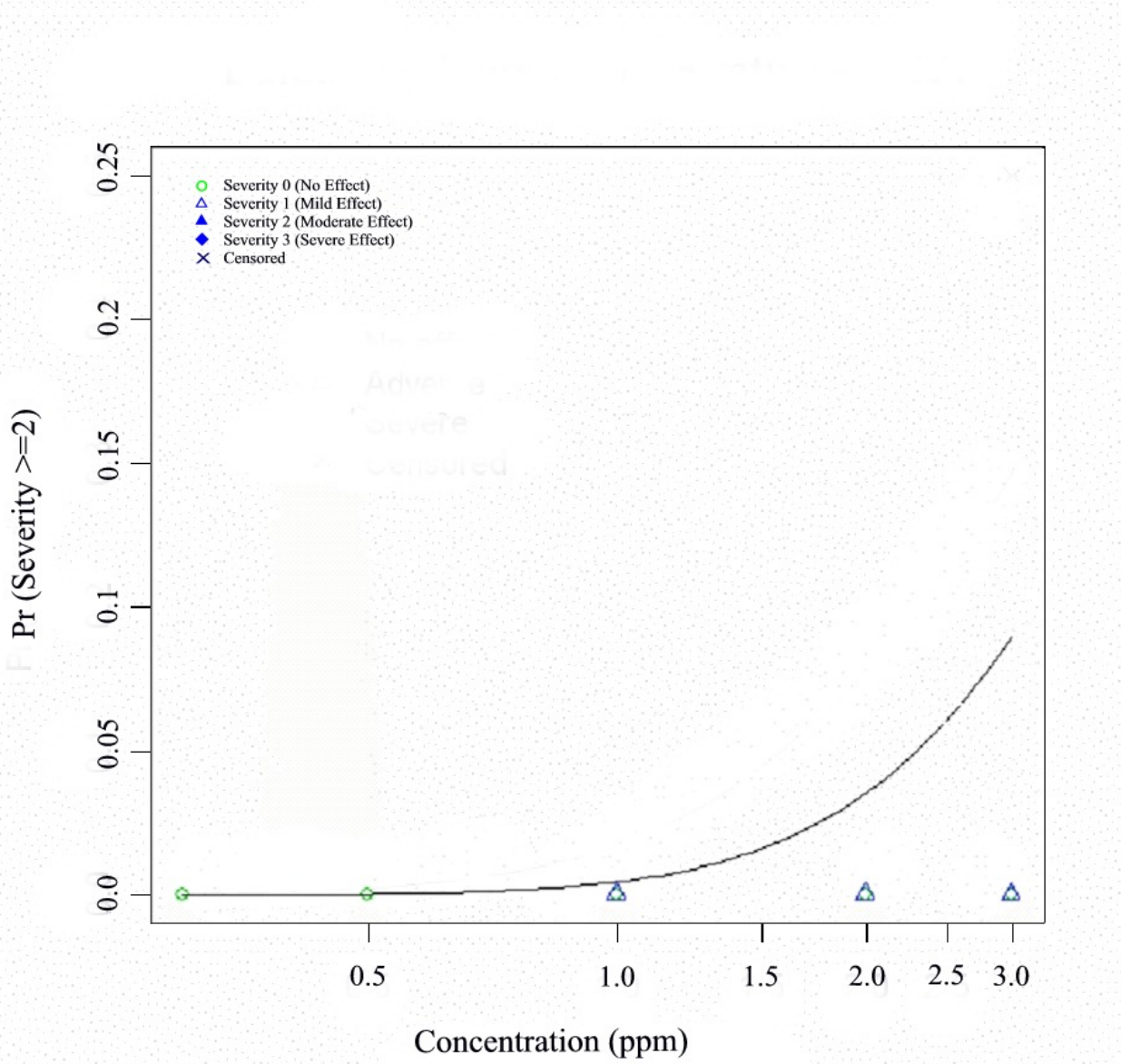


Figure 2. Probability Plot for Severity Level 2 (Severe Effects)



Comparison with Other Formaldehyde Acute Exposure Levels

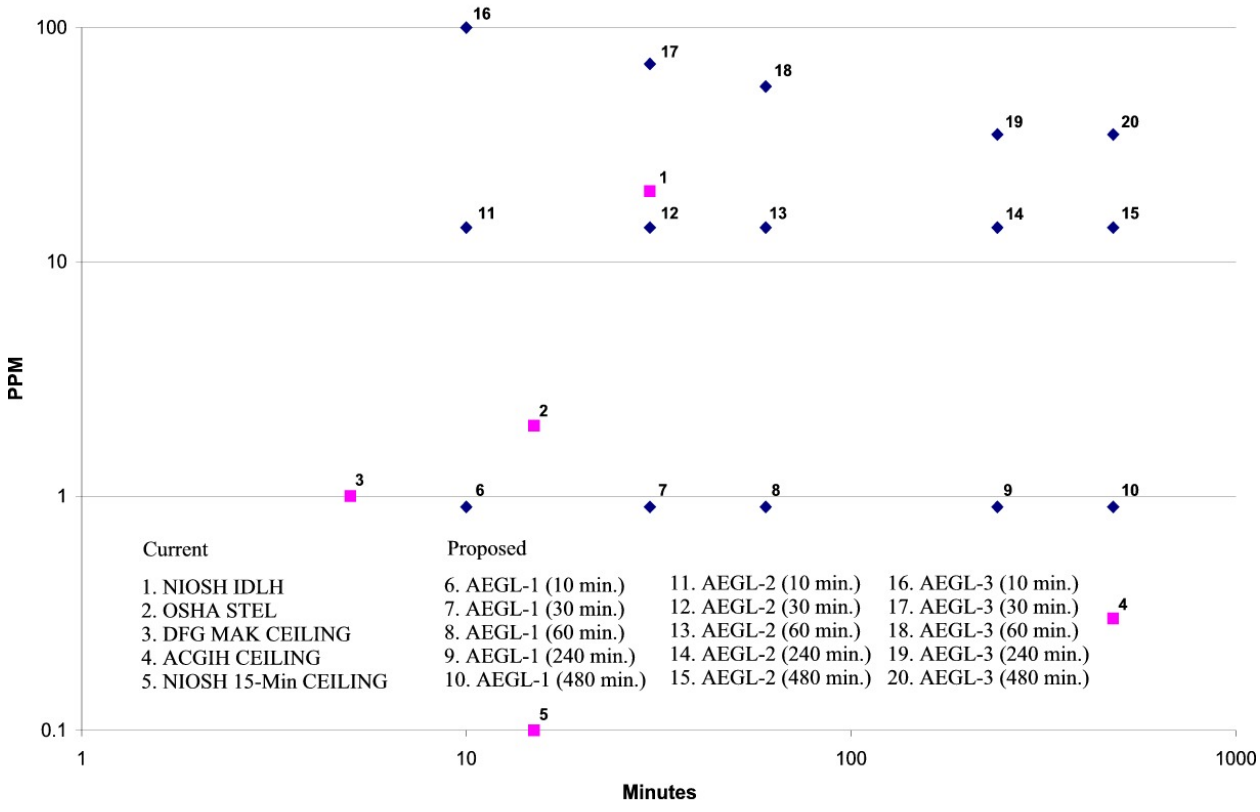
Current Values (ppm)

NIOSH IDLH	20
OSHA STEL	2
DFG MAK CEILING	1
ACGIH CEILING	0.3
NIOSH 15-Min CEILING	0.1

Proposed Values (ppm) (USEPA 2005)

	10 min	30 min	60 min	4 hr	8 hr
AEGL 1	0.9	0.9	0.9	0.9	0.9
AEGL 2	14	14	14	14	14
AEGL 3	100	70	56	35	35

Figure 3. Current and Proposed Formaldehyde Criteria



Conclusions

The CatReg Severity 1 (moderate effects) and 2 (severe effects) EC_{10} results for formaldehyde are in reasonable agreement with current criteria when viewed in context with their individual application. Given that the formaldehyde AEGLs depart from a Ct continuum, no direct comparison can be made.

Neither Activity nor health Status significantly contributes to explaining the categorical regression, i.e., responses were similar for those exposed either at rest or while exercising, and those who were healthy versus those who were asthmatic.

Human experimental data, categorical regression and the USEPA CatReg model provide useful information in analyzing exposure data, and should be considered in developing exposure criteria to formaldehyde.

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APPENDIX A
CATREG INPUT DATA

Study	Incid	Minutes	Hours	ppm	SevLo	SevHi	Activity	Status
Schachter87	8	40	0.67	2	0	0	R	H
Schachter87	5	40	0.67	2	1	1	R	H
Schachter87	2	40	0.67	2	2	2	R	H
Schachter87	9	40	0.67	2	0	0	E	H
Schachter87	3	40	0.67	2	1	1	E	H
Schachter87	2	40	0.67	2	2	2	E	H
Schachter87	1	40	0.67	2	3	3	E	H
Witek87	4	30	0.5	2	0	0	R	A
Witek87	7	30	0.5	2	1	1	R	A
Witek87	3	30	0.5	2	2	2	R	A
Witek87	1	30	0.5	2	3	3	R	A
Witek87	10	30	0.5	2	0	0	E	A
Witek87	2	30	0.5	2	1	1	E	A
Witek87	1	30	0.5	2	2	2	E	A
Witek87	1	30	0.5	2	3	3	E	A
Green87	16	55	0.92	3	0	1	E	H
Green87	6	55	0.92	3	2	3	E	H
Green87	13	55	0.92	3	0	1	E	A
Green87	3	55	0.92	3	2	3	E	A
Schachter86	8	40	0.67	2	0	0	R	H
Schachter86	4	40	0.67	2	1	1	R	H
Schachter86	2	40	0.67	2	2	2	R	H
Schachter86	3	40	0.67	2	3	3	R	H
Schachter86	7	40	0.67	2	0	0	E	H
Schachter86	7	40	0.67	2	1	1	E	H
Schachter86	1	40	0.67	2	2	2	E	H
Kulle93	6	180	3	0.5	0	0	R	H
Kulle93	4	180	3	0.5	1	1	R	H
Kulle93	14	180	3	1	0	0	E	H
Kulle93	5	180	3	1	1	1	E	H
Kulle93	8	180	3	2	0	0	E	H
Kulle93	8	180	3	2	1	1	E	H
Kulle93	3	180	3	2	2	2	E	H
Kulle93	2	180	3	3	0	0	R	H
Kulle93	6	180	3	3	1	1	R	H
Kulle93	1	180	3	3	3	3	R	H
Andersen 1979	13	300	5	0.24	0	0	R	H
Andersen 1979	3	300	5	0.24	1	1	R	H
Andersen 1979	11	300	5	0.41	0	0	R	H
Andersen 1979	5	300	5	0.41	1	1	R	H
Andersen 1979	1	300	5	0.82	0	0	R	H
Andersen 1979	15	300	5	0.82	1	1	R	H
Andersen 1979	1	300	5	1.63	0	0	R	H
Andersen 1979	15	300	5	1.63	1	1	R	H

A= Asthmatic or Otherwise Susceptible to Formaldehyde
E= Exercising
H= Healthy
R= Resting