EPA/635/R-09/011F www.epa.gov/iris

# TOXICOLOGICAL REVIEW

# OF

# TRICHLOROETHYLENE

# APPENDIX H

(CAS No. 79-01-6)

**In Support of Summary Information on the Integrated Risk Information System (IRIS)**

*September 2011*

# H. LIFETABLE ANALYSIS AND WEIGHTED LINEAR REGRESSION BASED ON RESULTS FROM CHARBOTEL ET AL. (2006)

## H.1. LIFETABLE ANALYSIS

A spreadsheet illustrating the extra-risk calculation for the derivation of the lower 95% bound on the effective concentration associated with a 1% extra risk ($LEC_{01}$) for RCC incidence is presented in Table H-1.

## H.2. EQUATIONS USED FOR WEIGHTED LINEAR REGRESSION OF RESULTS FROM CHARBOTEL ET AL. (2006) [SOURCE: ROTHMAN (1986), P. 343–344]

Linear model: $RR = 1 + bX$

where RR = risk ratio, $X$ = exposure, and $b$ = slope.

$b$ can be estimated from the following equation:

$$\hat{b} = \frac{\sum_{j=2}^{n} w_j x_j \hat{RR}_j - \sum_{j=2}^{n} w_j x_j}{\sum_{j=2}^{n} w_j x_j^{\,2}} \qquad \text{(Eq. H-1)}$$

where $j$ specifies the exposure category level and the reference category ($j = 1$) is ignored.

The standard error of the slope can be estimated as follows:

$$SE(\hat{b}) \approx \sqrt{\frac{1}{\sum_{j=2}^{n} w_j x_j^{\,2}}} \quad . \qquad \text{(Eq. H-2)}$$

The weights, $w_j$, are estimated from the CIs (as the inverse of the variance):

$$Var(\hat{RR}_j) \approx \hat{RR}_j^{\,2} Var[\ln(\hat{RR}_j)] \approx \hat{RR}_j^{\,2} \times \left[\frac{\ln(\overline{RR}_j) - \ln(\underline{RR}_j)}{2 \times 1.96}\right]^2 \qquad \text{(Eq. H-3)}$$

where $\overline{RR}_j$ is the 95% upper bound on the $RR_j$ estimate (for the $j$th exposure category) and $\underline{RR}_j$ is the 95% lower bound on the $RR_j$ estimate.

**Table H-1. Extra-risk calculation[a] for environmental exposure to 1.82 ppm TCE (the $LEC_{01}$ for RCC incidence)[b] using a linear exposure-response model based on the categorical cumulative exposure results of Charbotel et al. (2006), as described in Section 5.2.2.1.2.**

| A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Interval number (*i*)** | **Age interval** | **All cause mortality (× $10^5$/yr)** | **RCC incidence (× $10^5$/yr)** | **All cause hazard rate (*h**)** | **Prob. of surviving interval (*q*)** | **Prob. of surviving up to interval (*S*)** | **RCC cancer hazard rate (*h*)** | **Cond. prob. of RCC incidence in interval (*Ro*)** | **Exp. duration mid interval (*x*time)** | **Cum. exp. mid interval (*x*dose)** | **Exposed RCC hazard rate (*hx*)** | **Exposed all cause hazard rate (*h***x*)** | **Exposed prob. of surviving interval (*qx*)** | **Exposed prob. of surviving up to interval (*Sx*)** | **Exposed cond. prob. of RCC in interval (*Rx*)** |
| 1 | <1 | 685.2 | 0 | 0.0069 | 0.9932 | 1.0000 | 0.000000 | 0.000000 | 0.5 | 2.77 | 0.000000 | 0.0069 | 0.9932 | 1.0000 | 0.000000 |
| 2 | 1–4 | 29.9 | 0 | 0.0012 | 0.9988 | 0.9932 | 0.000000 | 0.000000 | 3 | 16.61 | 0.000000 | 0.0012 | 0.9988 | 0.9932 | 0.000000 |
| 3 | 5–9 | 14.7 | 0 | 0.0007 | 0.9993 | 0.9920 | 0.000000 | 0.000000 | 7.5 | 41.52 | 0.000000 | 0.0007 | 0.9993 | 0.9920 | 0.000000 |
| 4 | 10–14 | 18.7 | 0.1 | 0.0009 | 0.9991 | 0.9913 | 0.000005 | 0.000005 | 12.5 | 69.20 | 0.000006 | 0.0009 | 0.9991 | 0.9913 | 0.000006 |
| 5 | 15–19 | 66.1 | 0.1 | 0.0033 | 0.9967 | 0.9903 | 0.000005 | 0.000005 | 17.5 | 96.88 | 0.000006 | 0.0033 | 0.9967 | 0.9903 | 0.000006 |
| 6 | 20–24 | 94 | 0.2 | 0.0047 | 0.9953 | 0.9871 | 0.000010 | 0.000010 | 22.5 | 124.56 | 0.000013 | 0.0047 | 0.9953 | 0.9871 | 0.000013 |
| 7 | 25–29 | 96 | 0.7 | 0.0048 | 0.9952 | 0.9824 | 0.000035 | 0.000034 | 27.5 | 152.24 | 0.000049 | 0.0048 | 0.9952 | 0.9824 | 0.000048 |
| 8 | 30–34 | 107.9 | 1.6 | 0.0054 | 0.9946 | 0.9777 | 0.000080 | 0.000078 | 32.5 | 179.91 | 0.000117 | 0.0054 | 0.9946 | 0.9777 | 0.000114 |
| 9 | 35–39 | 151.7 | 3.2 | 0.0076 | 0.9924 | 0.9725 | 0.000160 | 0.000155 | 37.5 | 207.59 | 0.000245 | 0.0077 | 0.9924 | 0.9724 | 0.000237 |
| 10 | 40–44 | 231.7 | 6.3 | 0.0116 | 0.9885 | 0.9651 | 0.000315 | 0.000302 | 42.5 | 235.27 | 0.000504 | 0.0118 | 0.9883 | 0.9650 | 0.000484 |
| 11 | 45–49 | 352.3 | 11 | 0.0176 | 0.9825 | 0.9540 | 0.000550 | 0.000520 | 47.5 | 262.95 | 0.000919 | 0.0180 | 0.9822 | 0.9537 | 0.000869 |
| 12 | 50–54 | 511.7 | 17.3 | 0.0256 | 0.9747 | 0.9373 | 0.000865 | 0.000801 | 52.5 | 290.63 | 0.001507 | 0.0262 | 0.9741 | 0.9367 | 0.001393 |
| 13 | 55–59 | 734.8 | 26.2 | 0.0367 | 0.9639 | 0.9137 | 0.001310 | 0.001175 | 57.5 | 318.31 | 0.002375 | 0.0378 | 0.9629 | 0.9124 | 0.002127 |
| 14 | 60–64 | 1,140.1 | 36.2 | 0.0570 | 0.9446 | 0.8807 | 0.001810 | 0.001549 | 62.5 | 345.99 | 0.003409 | 0.0586 | 0.9431 | 0.8786 | 0.002909 |
| 15 | 65–69 | 1,727.4 | 44.6 | 0.0864 | 0.9173 | 0.8319 | 0.002230 | 0.001777 | 67.5 | 373.67 | 0.004358 | 0.0885 | 0.9153 | 0.8286 | 0.003456 |
| 16 | 70–74 | 2,676.4 | 49 | 0.1338 | 0.8747 | 0.7631 | 0.002450 | 0.001750 | 72.5 | 401.35 | 0.004961 | 0.1363 | 0.8726 | 0.7584 | 0.003518 |
| 17 | 75–59 | 4,193.2 | 51.6 | 0.2097 | 0.8109 | 0.6675 | 0.002580 | 0.001554 | 77.5 | 429.03 | 0.005407 | 0.2125 | 0.8086 | 0.6617 | 0.003223 |
| 18 | 80–84 | 6,717.2 | 44.4 | 0.3359 | 0.7147 | 0.5412 | 0.002220 | 0.001021 | 82.5 | 456.71 | 0.004809 | 0.3384 | 0.7129 | 0.5351 | 0.002183 |
| | | | | | | | ***Ro* =** | 0.010736 | | | | | | ***Rx* =** | 0.020586 |
| **Extra risk = (*Rx* – *Ro*)/(1 – *Ro*) = 0.00996** | | | | | | | | | | | | | | | |

Column A: interval index number ($i$).
Column B: 5-year age interval (except <1 and 1–4) up to age 85.
Column C: all-cause mortality rate for interval $i$ ($\times 10^5$/year) [2004 data from CDC (2007)].
Column D: RCC incidence rate for interval $i$ ($\times 10^5$/year) (2001–2005 SEER data [http://seer.cancer.gov]).
Column E: all-cause hazard rate for interval $i$ ($h^*_i$) [= all-cause mortality rate × number of years in age interval].[c]
Column F: probability of surviving interval $i$ without being diagnosed with RCC ($q_i$) [= $\exp(-h^*_i)$].
Column G: probability of surviving up to interval $i$ without having been diagnosed with RCC ($S_i$) [$S_1 = 1$; $S_i = S_{i-1} \times q_{i-1}$, for i > 1].
Column H: RCC incidence hazard rate for interval $i$ ($h_i$) [= RCC incidence rate × number of years in interval].
Column I: conditional probability of being diagnosed with RCC in interval $i$ [= $(h_i/h^*_i) \times S_i \times (1-q_i)$] (i.e., conditional upon surviving up to interval $i$ without having been diagnosed with RCC) [Ro, the background lifetime probability of being diagnosed with RCC = the sum of the conditional probabilities across the intervals].
Column J: exposure duration (in years) at mid-interval ($x$time).
Column K: cumulative exposure mid-interval ($x$dose) [= exposure level (i.e., 1.82 ppm) × 365/240 × 20/10 × $x$time] (365/240 × 20/10 converts continuous environmental exposures to corresponding occupational exposures).
Column L: RCC incidence hazard rate in exposed people for interval $i$ ($hx_i$) [= $h_i \times (1 + \beta \times x\text{dose})$, where $\beta = 0.001205 + (1.645 \times 0.0008195) = 0.002554$] [0.001205 per ppm × year is the regression coefficient obtained from the weighted linear regression of the categorical results (see Section 5.2.2.1.2). To estimate the $LEC_{01}$ (i.e., the 95% lower bound on the continuous exposure giving an extra risk of 1%), the 95% upper bound on the regression coefficient is used (i.e., MLE + 1.645 × SE).
Column M: all-cause hazard rate in exposed people for interval $i$ ($h^*x_i$) [= $h^*_i + (hx_i - h_i)$].
Column N: probability of surviving interval $i$ without being diagnosed with RCC for exposed people ($qx_i$) [= $\exp(-h^*x_i)$].
Column O: probability of surviving up to interval $i$ without having been diagnosed with RCC for exposed people ($Sx_i$) [$Sx_1 = 1$; $Sx_i = Sx_{i-1} \times qx_{i-1}$, for i > 1].
Column P: conditional probability of being diagnosed with RCC in interval $i$ for exposed people [= $(hx_i/h^*x_i) \times Sx_i \times (1-qx_i)$] (Rx, the lifetime probability of being diagnosed with RCC for exposed people = the sum of the conditional probabilities across the intervals).

[a]Using the methodology of BEIR IV (1988).
[b]The estimated 95% lower bound on the continuous exposure level of TCE that gives a 1% extra lifetime risk of RCC.
[c]For the cancer incidence calculation, the all-cause hazard rate for interval $i$ should technically be the rate of either dying of any cause or being diagnosed with the specific cancer during the interval, i.e., the all-cause mortality rate for the interval + the cancer-specific incidence rate for the interval—the cancer-specific mortality rate for the interval [so that a cancer case isn't counted twice, i.e., upon diagnosis and upon death]) × number of years in interval. This adjustment was ignored here because the RCC incidence rates are small compared with the all-cause mortality rates.