**Additional file 4. Dose-response analysis by Stata/SE 14.0 (commands).**

. gen loghr=ln( hr )

. gen seloghr=(ln( ub )-ln( lb ))/(2\* invnormal(.975))

. bysort id :gen tmaoc = tmao- tmao[1]

. mkspline tmaocs =tmaoc, nk(3) cubic

. mkspline tmaos = tmao, nk(3) cubic

. mvmeta\_make glst loghr tmaocs1 tmaocs2, cov( n case ) se( seloghr ) pfirst( id studyt) saving( ssest\_spline ) replace by( id ) names( b V )

preserve

. use ssest\_spline.dta, clear

. mvmeta b V, mm i2

testparm btmaocs2

capture estimates save mvmeta, replace

. restore

. estimates use mvmeta

summarize tmaos1 tmaos2 if tmao

predictnl loghr\_sp = \_b[btmaocs1]\*(tmaos1-4.17)+\_b[btmaocs2]\*(tmaos2-1.14),ci(low up)

gen hrs = exp(loghr\_sp)

gen lbs = exp(low)

gen ubs = exp(up)

glst loghr tmaoc, cov(n case) se(seloghr) pfirst(id studyt) ts(r)

predictnl loghr\_line = \_b[tmaoc]\*(tmao-4.17)

gen hrl = exp(loghr\_line)

twoway (line hrl tmao, sort lc(black) lp(-)) (line hrs lbs ubs tmao, sort lw(thick thick thick) lc(black black black) lp(l longdash longdash)), yscale(log) ytitle(“Hazard Ratio”) xtitle (“Trimetlylamine Oxide”) scheme(s1mono) xlabel(0(1)10) xmtick(0(.1)10) ymtick(0(.1)2) ylabel(1 2 3,format(%3.2fc) angle(horiz)) legend(label(1 “Linear Model”) label(2 “Spline Model”) order(1 2) ring(0) pos(11) col(1) ) plotregion(style(none))