{**Appendix B. Supplementary data**

**A physiologically based toxicokinetic model for inhaled ethylene and ethylene oxide in mouse, rat, and human**

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Model code for uninterrupted exposures of mice, rats or humans to ET and/or EO

using the program Berkeley Madonna X (Mach-O), version 8.3.22 for
Mac OS X 10.6.8}

{For parameters and their abbreviations see Tables 1, 2, 3, and 10 in the article.

A question mark stays for a number to be put in here.}

METHOD RK4

STARTTIME = 0

STOPTIME = ?

DT = 0.0001

{DTOUT = 0.1 {Printed time steps}}

{Body weights and number of exposed animals or humans}

BW = ? {kg, body weight of one reference animal or human (see Table 1}

BWe = ? {kg, average body weight of one exposed animal or human}

Num = ? {number of animals or humans exposed together in one chamber}

{Flows, Table 1}

Qalv= ? /BW \*BWe\* Num {L/h, 1.2 (mouse), 7.02 (rat), 300 (human)}

Qcard= ? /BW\*BWe\* Num {L/h, 1.02 (mouse), 5.04 (rat), 372 (human)}

Qr = ? \* Qcard {L/h, 0.355 (mouse), 0.355 (rat), 0.285 (human)}

Qk = ? \* Qcard {L/h, 0.155 (mouse), 0.155 (rat), 0.155 (human)}

Qm= ? \* Qcard {L/h, 0.223 (mouse), 0.223 (rat), 0.250 (human)}

Qa= ? \* Qcard {L/h, 0.017 (mouse), 0.017 (rat), 0.050 (human)}

QL= ? \* Qcard {L/h, 0.250 (mouse), 0.250 (rat), 0.260 (human)}

{Volumes, Table 1}

Vch = ? - (BWe\* Num) {L, experimental volume of the closed-chamber with ET-exposed mice, rats, or humans}

VEOch = ? - (BWe\* Num) {L, experimental volume of the closed-chamber with EO-exposed mice, rats, or humans}

Vart = ? \*BWe\* Num {L, 0.0159 (mouse), 0.0241 (rat), 0.0257 (human)}

Vvnb = ? \*BWe\* Num {L, 0.0331 (mouse), 0.050 (rat), 0.0533 (human)}

Vr = ? \*BWe\* Num {L, 0.026 (mouse), 0.0377 (rat), 0.038 (human)}

Vk = ? \*BWe\* Num {L, 0.0167 (mouse), 0.0073 (rat), 0.0044 (human)}

Vp = ? \*BWe\* Num {L, 0.0073 (mouse), 0.005 (rat), 0.0076 (human)}

Vm = ? \*BWe\* Num {L, 0.66 (mouse), 0.676 (rat), 0.541 (human)}

Va = ? \*BWe\* Num {L, 0.10 (mouse), 0.07 (rat), 0.19 (human)}

VL = ? \*BWe\* Num {L, 0.055 (mouse), 0.04 (rat), 0.026 (human)}

{Water contents, Table 1}

wfb = ?

wfr = ?

wfk = ?

wfp = ?

wfm = ?

wfa = ?

wfL = ?

{Blood-to-air and tissue-to-blood partition coeficients of ET, Table 1}

Pbair = ?

Prb = ?

Pkb = ?

Ppb = ?

Pmb = ?

Pab = ?

PLb = ?

{Species-independent blood-to-air and tissue-to-blood partition coeficients of EO, Table 1}

PEObair = 61

PEOrb = 1.03

PEOkb = 1.03

PEOpb = 1.03

PEOmb = 1.08

PEOab = 0.70

PEOLb = 0.89

{Wash-in-wash-out effect, Table 1}

fET = ?

fEO = ?

{ Species-independent rate constants of non-enzymatic pozesses, Table 2}

kEOG = 0.01248 {L/(mmol GSH\*h)}

kEOh = 0.06 {1/h}

{Metabolism of ET in liver, Table 2}

k3 = ? {1/h}

k4 = ? {1/h}

Kmmo = ? {mmol/L in venous liver blood}

ke = ? {1/h}

CYPo = ? {mmol/kg liver}

{Metabolism of EO, Table 2}

{EH in liver}

VmaxEOEH = ? {mmol/h/kg liver}

KmapEO = ? {mmol/L}

KmihEO = ? {mmol/L}

{GST in liver}

VmaxgstL = ? {mmol/h/kg liver}

KmEOL = 9 {mmol/L, species-independent}

KmgshL = 0.1 {mmol/L species-independent}

kdgshL = 0.2 {1/h, species-independent}

CgshoL = ? {mmol/L}

{GST in lung (p)}

Vmaxgstp = ? {mmol/h/kg lung}

KmEOp = 9 {mmol/L, species-independent}

Kmgshp = 0.1 {mmol/L, species-independent}

kdgshp = ? { 1/h}

Cgshop = ? {mmol/L}

{GST in kidneys}

Vmaxgstk = ? {mmol/h/kg kidney}

KmEOk = 9 {mmol/L, species-independent}

Kmgshk = 0.1 {mmol/L, species-independent}

kdgshk = 0.2 {1/h, species-independent}

Cgshok = ? {mmol/L}

{GST in RPTG}

Vmaxgstr = ? {mmol/h/kg RPTG}

KmEOr = 9 {mmol/L, species-independent}

Kmgshr = 0.1 {mmol/L, species-independent}

Kdgshr = 0.2 {1/h, species-independent}

Cgshor = ? {mmol/L}

{GST in blood}

Vmaxgstb = ? {mmol/h/L blood}

KmEOb = 9 {mmol/L, species-independent}

Kmgshb = 0.1 {mmol/L, species-independent}

Kdgshb = 0.2 {1/h, species-independent}

Cgshob = ? {mmol/L}

{Hb-adducts, Table 3}

khb = ? {L/h/g Hb, rate constant of formation of HEV; mouse, 0.8416/10000; rat, 0.46/10000; human, 0.45/10000}

ter = ? {h, lifespan of Hb; mouse: 960; Rat: 1440; Human: 3024}

{ DNA-Adducts}

kDNA = 0.94/10000 {L/h/g DNA, rate constant of formation of HEG in DNA; all species}

keG = ? {1/h, depurination rate constant of HEG; mouse and and rat: 0.011, human: 0.0077; Table 3}

{Initial concentration of ET; for abbreviations and dimensions see Table 10}

INIT Cair = ? {mmol ET/L air; the concentrations mmol/L air is obtained as the product of ppm in atmosphere with 0.0000409.}

INIT Cp = 0

INIT Cart = 0

INIT Cvnb = 0

INIT Cr = 0

INIT Ck = 0

INIT Cm = 0

INIT Ca = 0

INIT CL = 0

INIT CYP = CYPo

{Initial concentration of EO; for abbreviations and dimensions see Table 10}

INIT CEOair = ? {mmol EO/L air; the concentrations mmol/L air is obtained as the product of ppm in atmosphere with 0.0000409.}

INIT CEOp = 0

INIT CEOart = 0

INIT CEOvnb = 0

INIT CEOr = 0

INIT CEOk = 0

INIT CEOm = 0

INIT CEOa = 0

INIT CEOL = 0

{Initial GSH concentrations; For abbreviations and dimensions see Tables 2 and 10}

INIT Cgshp = Cgshop

INIT Cgshart = Cgshob

INIT Cgshvnb = Cgshob

INIT Cgshr = Cgshor

INIT Cgshk = Cgshok

INIT CgshL = CgshoL

{Differential equations}

{ET}

{Air of closed exposure system}

d/dt(Cair) =(Qalv\*(Cp/(Ppb\*Pbair)-Cair\*fET))/Vch {mmol/L air}

{Lung}

d/dt (Cp) =(Qalv\*(Cair\*fET-Cp/(Ppb\*Pbair))+Qcard\*(Cvnb-Cp/Ppb))/Vp

{Arterial blood}

d/dt (Cart) =Qcard\*(Cp/Ppb-Cart)/Vart

{Venous blood}

d/dt (Cvnb) =(Qr\*Cr/Prb+Qm\*Cm/Pmb+Qk\*Ck/Pkb+Qa\*Ca/Pab+QL\*CL/PLb- Qcard\*Cvnb)/Vvnb

{RPTG}

d/dt(Cr) =(Qr\*(Cart-Cr/Prb))/Vr

{Kidneys}

d/dt (Ck) =(Qk\*(Cart-Ck/Pkb))/Vk

{Muscle}

d/dt(Cm) =(Qm\*(Cart-Cm/Pmb))/Vm

{FAT}

d/dt(Ca) =(Qa\*(Cart-Ca/Pab))/Va

{Liver}

d/dt(CYP) =ke\*(CYPo-CYP)-k4\*CYP\*CL/(PLb\*Kmmo+CL) {mmol/h/kg liver}

d/dt(CL) =(QL\*(Cart-CL/PLb)-k3\*CYP\*VL\*CL/(PLb\*Kmmo+CL))/VL

{EO}

{Air of closed exposure system}

d/dt(CEOair) =(Qalv\*(CEOp/(PEOpb\*PEObair)-CEOair\*fEO))/VEOch {mmol/L air}

{Lung}

d/dt (CEOp) =(Qalv\*(CEOair\*fEO-CEOp/(PEOpb\*PEObair))+Qcard\*(CEOvnb-CEOp/PEOpb)-kEOh\*CEOp\*Vp\*wfp-kEOG\*Vp\*Cgshp\*CEOp-CEOp\*Cgshp\* Vmaxgstp\*Vp/(Kmgshp\*CEOp+KmEOp\*Cgshp+CEOp\*Cgshp))/Vp

{Arterial Blood}

d/dt (CEOart) =(Qcard\*(CEOp/PEOpb-CEOart)-kEOh\*CEOart\*Vart\*wfb-CEOart\* Cgshart\*Vmaxgstb\*Vart/(Kmgshb\*CEOart+KmEOb\*Cgshart+CEOart\*Cgshart)- kEOG\*Vart\*Cgshart\*CEOart)/Vart

{Venous Blood}

d/dt (CEOvnb) = (Qr\*CEOr/PEOrb+Qm\*CEOm/PEOmb+Qa\*CEOa/PEOab+QL\*CEOL/PEOLb +Qk\*CEOk/PEOkb-Qcard\*CEOvnb-kEOh\*CEOvnb\*Vvnb\*wfb-CEOvnb\*Cgshvnb\* Vmaxgstb\*Vvnb/(Kmgshb\*CEOvnb+KmEOb\*Cgshvnb+CEOvnb\*Cgshvnb)- kEOG\*Vvnb\*Cgshvnb\*CEOvnb)/Vvnb

{RPTG}

d/dt(CEOr) =(Qr\*(CEOart-CEOr/PEOrb)-kEOh\*CEOr\*Vr\*wfr-CEOr\*Cgshr\*Vmaxgstr\*Vr/(Kmgshr\*CEOr+KmEOr\*Cgshr+CEOr\*Cgshr)- kEOG\*Vr\*Cgshr\*CEOr)/Vr

{Kidneys}

d/dt (CEOk) =(Qk\*(CEOart-CEOk/PEOkb)-kEOh\*CEOk\*Vk\*wfk-CEOk\*Cgshk\*Vmaxgstk\*Vk/(Kmgshk\*CEOk+KmEOk\*Cgshk+CEOk\*Cgshk)- kEOG\*Vk\*Cgshk\*CEOk)/Vk

{Muscle}

d/dt(CEOm) =(Qm\*(CEOart-CEOm/PEOmb)-kEOh\*CEOm\*Vm\*wfm)/Vm

{Fat}

d/dt(CEOa) =(Qa\*(CEOart-CEOa/PEOab)-kEOh\*CEOa\*Va\*wfa)/Va

{Liver}

d/dt(CEOL) =(QL\*(CEOart-CEOL/PEOLb)+Qih\*(0.5\*((CEOL-KmihEO+(k3\*CYP\*VL\*CL)/(Qih\*(CL+PLb\*Kmmo))-VmaxEOEH\*VL/Qih)+SQRT((CEOL-KmihEO+(k3\*CYP\*VL\*CL)/(Qih\*(CL+PLb\*Kmmo))-VmaxEOEH\*VL/Qih)^2+4\*KmihEO\*(CEOL + (k3 \* CYP\*VL\* CL)/(Qih\*(CL+PLb\*Kmmo)))))-CEOL)-CEOL\*CgshL\*VmaxgstL\*VL/(KmgshL\*CEOL+KmEOL\*CgshL+CEOL\*CgshL)- kEOG\*VL\*CgshL\*CEOL-kEOh\*CEOL\*VL\*wfL)/VL

Qih =VmaxEOEH\*VL/(KmapEO-KmihEO)

{GSH-metabolism}

{Lung}

d/dt(Cgshp) =(kdgshp\*Vp\*(Cgshop-Cgshp)-CEOp\*Cgshp\*Vmaxgstp\*Vp/(Kmgshp\*CEOp+KmEOp\*Cgshp+CEOp\*Cgshp)- kEOG\*Vp\*Cgshp\*CEOp)/Vp

{Arterial blood}

d/dt(Cgshart) =(kdgshb\*Vart\*(Cgshob-Cgshart)-CEOart\*Cgshart\*Vmaxgstb\*Vart/(Kmgshb\*CEOart+KmEOb\*Cgshart+CEOart\*Cgshart)-kEOG\*Vart\*Cgshart\*CEOart)/Vart

{Venous blood}

d/dt(Cgshvnb) =(kdgshb\*Vvnb\*(Cgshob-Cgshvnb)-CEOvnb\*Cgshvnb\*Vmaxgstb\*Vvnb/(Kmgshb\*CEOvnb+KmEOb\*Cgshvnb+CEOvnb\*Cgshvnb)-kEOG\*Vvnb\*Cgshvnb\*CEOvnb)/Vvnb

{RPTG}

d/dt(Cgshr) =(kdgshr\*Vr\*(Cgshor-Cgshr)-CEOr\*Cgshr\*Vmaxgstr\*Vr/(Kmgshr\*CEOr+KmEOr\*Cgshr+CEOr\*Cgshr)- kEOG\*Vr\*Cgshr\*CEOr)/Vr

{Kidneys}

d/dt(Cgshk) =(kdgshk\*Vk\*(Cgshok-Cgshk)- CEOk\*Cgshk\*Vmaxgstk\*Vk/(Kmgshk\*CEOk+KmEOk\*Cgshk+CEOk\*Cgshk)- kEOG\*Vk\*Cgshk\*CEOk)/Vk

{Liver}

d/dt(CgshL) =(kdgshL\*VL\*(CgshoL-CgshL)-CEOL\*CgshL\*VmaxgstL\*VL/(KmgshL\*CEOL+KmEOL\*CgshL+CEOL\*CgshL)- kEOG\*VL\*CgshL\*CEOL)/VL

{Hb-Adducts; Inits and diff.-equations}

Init CTHB = 0 {mmol HEV/g HB}

Init CHB = 0 {mmol HEV/g Hb}

d/dt(CTHB) = (Vart \* CEOart + Vvnb\* CEOvnb) \* khb/(Vart + Vvnb)

d/dt(CHB) = (Vart \* CEOart + Vvnb\* CEOvnb) \* khb/ (Vart + Vvnb) - CTHB/ter
{solution gives CHB at time t≤ter}

{DNA-Adducts; Inits and diff.-equations}

Init CDNA = 0 {mmol HEG/g DNA, DNA-Adduct level}

d/dt(CDNA) = ((Vart \* CEOart + Vvnb\* CEOvnb)\* kDNA - (Vart + Vvnb)\*CDNA\* keG) /(Vart + Vvnb)

{Some variables, given as functions of time}

{ET concentrations}

Cairppm = Cair \*24450 {ppm, ET in air}

{EO concentrations}

CEOairppm= CEOair \*24450 {ppm, EO in air}

CEOvbmgL = CEOvnb \* 44.05 {mg/L, EO in venous blood}

CEOvbµgL = CEOvnb \* 44.05\*1000 {µg/L, EO in venous blood}

CEOvbµmolL = CEOvnb \*1000 {µmol/L, EO in venous blood}

CEOvbnmolL = CEOvbµmolL \*1000 {nmol/L, EO in venous blood}

{Adduct levels}

nCHB = CHB \* 1000000 {nmol HEV/g Hb, HEV level }

nCDNA = CDNA \* 1000000 {nmol HEG/g DNA, HEG level}

GDNA = nCDNA/0.663634451 {pmol HEG/µmol Gua-base, HEG level}