APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99– 499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation   [ ] Oral
Duration: [X] Acute   [ ] Intermediate   [ ] Chronic
Graph Key: 3
Species: Rat

Minimal Risk Level: 0.02   [ ] mg/kg/day   [ ]   ppm   [X] mg/m^3

Reference: Kimmerle G. 1976. Subchronic inhalation toxicity of azinphos-methyl in rats. Arch Toxicol 35:83-89.

Experimental design: In this study (Kimmerle 1976), groups of 10 male and 10 female SPF Wistar rats were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 μm. The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks and determinations of hematology, serum glutamic-oxalacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase, urea, creatinine, and bilirubin were conducted after 12 weeks of exposure. At study termination, animals were sacrificed for gross examination. The thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads were weighed and examined histologically and brain AChE activity was determined.

Effect noted in study and corresponding doses: There were no significant changes in appearance or behavior of male or female rats. Male rats in the 4.72 mg/m^3 group showed a 20% reduction in body weight gain during the 12-week exposure period. Although body weight was not reported on week 2, on week 4, body weight gain in male rats in the 4.72 mg/m^3 group was 60% that in control animals. After 2 weeks of exposure, erythrocyte AChE activity was reduced by 25 and 18% in male and female rats, respectively, in the 4.72 mg/m^3 group, but not at lower concentrations. There were no biologically significant reductions in plasma ChE activity at any of the doses tested.

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 1.24 mg/m^3 and a LOAEL of 4.72 mg/m^3 for decreased erythrocyte AChE activity after 2 weeks of exposure.

[X] NOAEL   [ ] LOAEL

Uncertainty Factors used in MRL derivation:

        [ ] 10 for use of a LOAEL
        [X]   3 for extrapolation from animals to humans with dosimetric adjustments
        [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: As per MRL guidance from ATSDR, a 5–7-day duration adjustment is not conducted for acute inhalation

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exposures. Thus, the NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure (NOAEL$_{[ADJ]}$) as follows:

NOAEL$_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours
NOAEL$_{[ADJ]}$ = 0.31 mg/m^3

The human equivalent concentration (HEC) of the NOAEL$_{[ADJ]}$ was calculated using the equations below. The RDDR$_{[ER]}$ is the regionally deposited dose ratio for the extrarespiratory effects. It is calculated using EPA's software (version 2.3) for calculating RDDRs (EPA 1994b) and particle size and body weight data from Kimmerle (1976). A presentation of the equations and assumptions used to calculate the RDDR can be found in EPA (1994b).

NOAEL$_{[HEC]}$ = NOAEL$_{[ADJ]}$ x RDDR$_{[ER]}$
NOAEL$_{[HEC]}$ = 0.31 mg/m^3 x 1.626
NOAEL$_{[HEC]}$ = 0.50 mg/m^3

An RDDR$_{ER}$ of 1.626 was estimated using the default parameters and body weight data presented in Table A-1.

Table A-1. Default Parameters Used in the Derivation of RDDR$_{ER}$

Parameter	Humans	Rats
Body weight (kg)	70.00	0.182[a]
Minute volume (L)	13.80	0.139
ET area (cm^2)[b]	200.00	15.00
TB area (cm^2)[c]	3,200.00	22.50
PU area (m^2)[d]	54.00	0.34

[a]2-week body weight value estimated from Kimmerle (1976)
[b]Extrathoracic respiratory tract region
[c]Tracheobronchial respiratory tract region
[d]Pulmonary respiratory tract region

RDDR$_{ER}$ = regionally deposited dose ratio for the extrarespiratory effects

Based on the information provided by Kimmerle (1976) it was assumed that the sizes of the aerosol particles were log-normally distributed in a manner such that 1.5% of these were <0.5 μm and 1.5% were >1.5 μm. Based on these assumptions, a geometric mean and geometric standard deviation of 0.9 and 0.23 μm, respectively, were calculated. These values were used to calculate a Mass Median Aerodynamic Diameter (MMAD) of 0.88 μm using the recommended equation in Table H-2 (shown below) of the guidance document Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

$$MMAD = CMAD \; e(3[\ln \text{ variance}]^2)$$

No conversion is required for the geometric standard deviation and the geometric standard deviation of 0.23 was used. CMAD is the count median aerodynamic diameter (0.9 μm).

The NOAEL$_{[HEC]}$ of 0.50 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustment and 10 for human variability), resulting in an acute-

duration inhalation MRL of 0.02 mg/m^3. Application of the benchmark dose methodology to the data from Kimmerle (1976) was considered, but the data were presented as means without standard errors or standard deviations. Without these measures, the benchmark dose methodology could not be applied.

Was a conversion used from intermittent to continuous exposure? Yes, animals were exposed 6 hours/day, 5 days/week.

NOAEL$_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours
NOAEL$_{[ADJ]}$ = 0.31 mg/m^3

Other additional studies or pertinent information that lend support to this MRL: EPA (1978a) reported a 41% (range 27–59%) reduction in blood ChE activity in rats exposed to guthion aerosols (39 mg/m^3) for 1 hour. The consistent observation of reduced ChE activity in the two available inhalation studies is in agreement with the observations made in a number of studies with guthion administered orally to rats and dogs during acute (Astroff and Young 1998; Pasquet et al. 1976), intermediate (Holzum 1990; Sheets et al. 1997), and chronic (Allen et al. 1990; Schmidt and Chevalier 1984) exposures.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation   [ ] Oral
Duration: [ ] Acute   [X] Intermediate   [ ] Chronic
Graph Key: 7
Species: Rat

Minimal Risk Level: 0.01   [ ] mg/kg/day   [ ]   ppm [X] mg/m^3

Reference: Kimmerle G. 1976. Subchronic inhalation toxicity of azinphos-methyl in rats. Arch Toxicol 35:83-89.

Experimental design: In this study (Kimmerle 1976), groups of 10 male and 10 female SPF Wistar rats were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 μm (Kimmerle 1976). The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks and determinations of hematology, SGOT, SGPT, alkaline phosphatase, urea, creatinine, and bilirubin were conducted after 12 weeks of exposure. At study termination, animals were sacrificed for gross examination. The thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads were weighed and examined histologically and brain AChE activity was determined.

Effect noted in study and corresponding doses: There were no significant changes in appearance or behavior of male or female rats. Male rats in the 4.72 mg/m^3 group showed a 20% reduction in body weight gain during the 12-week exposure period. No effects were detected in the examined hematological and serum clinical chemistry parameters. There were no observed differences in absolute or relative organ weights or morphological alterations in organs or tissues in any of the rats. From week 4 to week 12, erythrocyte AChE activity was reduced by 29–48% in male and 26–39% in female rats in the 4.72 mg/m^3 group. There were no additional reductions in erythrocyte AChE activity beyond week 4. Reductions in erythrocyte AChE activity in rats exposed to guthion doses <4.72 mg/m^3 were 17% or less and are not considered an adverse effect. The investigator noted that brain ChE activity was not reduced at any of the concentrations tested, but no data were shown.

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 1.24 mg/m^3 and LOAEL of 4.72 mg/m^3 for decreased erythrocyte AChE activity.

[X] NOAEL   [ ] LOAEL

Uncertainty Factors used in MRL derivation:

       [   ] 10 for use of a LOAEL
       [X]   3 for extrapolation from animals to humans with dosimetric adjustments
       [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

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If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The
NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure (NOAEL[ADJ]) as follows:

NOAEL$_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours x 5 days/7 days
NOAEL$_{[ADJ]}$ = 0.22 mg/m^3

The human equivalent concentration (HEC) of the NOAEL$_{[ADJ]}$ was calculated using the equations below.
The RDDR$_{[ER]}$ is the regionally deposited dose ratio for the extrarespiratory effects. It is calculated using
EPA's software (version 2.3) for calculating RDDRs (EPA 1994b) and particle size and body weight data
from Kimmerle (1976). A presentation of the equations and assumptions used to calculate the RDDR can
be found in EPA (1994b).

NOAEL$_{[HEC]}$ = NOAEL$_{[ADJ]}$ x RDDR$_{[ER]}$
NOAEL$_{[HEC]}$ = 0.22 mg/m^3 x 1.695
NOAEL$_{[HEC]}$ = 0.37 mg/m^3

An RDDR$_{ER}$ of 1.695 was estimated using the default parameters and body weight data presented in
Table A-2.

Table A-2. Default Parameters Used in the Derivation of RDDR$_{ER}$

Parameter	Humans	Rats
Body weight (kg)	70.00	0.253[a]
Minute volume (L)	13.80	0.182
ET area (cm^2)[b]	200.00	15.00
TB area (cm^2)[c]	3,200.00	22.50
PU area (m^2)[d]	54.00	0.34

[a]12-week body weight value from Kimmerle (1976)
[b]Extrathoracic respiratory tract region
[c]Tracheobronchial respiratory tract region
[d]Pulmonary respiratory tract region

RDDR$_{ER}$ = regionally deposited dose ratio for the extrarespiratory effects

Based on the information provided by Kimmerle (1976), it was assumed that the sizes of the aerosol
particles were log-normally distributed in a manner such that 1.5% of these were <0.5 μm and 1.5% were
>1.5 μm. Based on these assumptions, a geometric mean and geometric standard deviation of 0.9 and
0.23 μm, respectively, were calculated. These values were used to calculate a MMAD of 0.88 μm using
the recommended equation in Table H-2 of the guidance document Methods for Derivation of Inhalation
Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

$$MMAD = CMAD \; e(3[\ln \text{variance}]^2)$$

No conversion is required for the geometric standard deviation and the geometric standard deviation of
0.23 was used. CMAD is the count median aerodynamic diameter (0.9 μm).

The NOAEL$_{[HEC]}$ of 0.37 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from
animals to humans using dosimetric adjustment and 10 for human variability), resulting in an
intermediate-duration inhalation MRL of 0.01 mg/m^3. Application of the benchmark dose methodology

to the data from Kimmerle (1976) was considered, but the data were presented as means without standard errors or standard deviations. Without these measures, the benchmark dose methodology could not be applied.

Was a conversion used from intermittent to continuous exposure? Yes, animals were exposed 6 hours/day, 5 days/week.

$NOAEL_{[ADJ]}$ = 1.24 mg/m^3 x 6 hours/24 hours x 5 days/7 days
$NOAEL_{[ADJ]}$ = 0.22 mg/m^3

Other additional studies or pertinent information that lend support to this MRL: EPA (1978a) reported a 41% (range 27–59%) reduction in blood ChE activity in rats exposed to guthion aerosols (39 mg/m^3) for 1 hour. The consistent observation of reduced ChE activity in the two available inhalation studies is in agreement with the observations made in a number of studies with guthion administered orally to rats and dogs during acute (Astroff and Young 1998; Pasquet et al. 1976), intermediate (Holzum 1990; Sheets et al. 1997), and chronic (Allen et al. 1990; Schmidt and Chevalier 1984) exposures.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [X] Inhalation   [ ] Oral
Duration: [ ] Acute   [ ] Intermediate   [X] Chronic
Graph Key: 7
Species: Rat

Minimal Risk Level: 0.01   [ ] mg/kg/day [ ]   ppm [X] mg/m^3

Reference: Kimmerle G. 1976. Subchronic inhalation toxicity of azinphos-methyl in rats. Arch Toxicol 35:83-89.

Experimental design: In this study (Kimmerle 1976), groups of 10 male and 10 female SPF Wistar rats were exposed to aerosolized guthion at 0.195, 1.24, or 4.72 mg/m^3, 6 hours/day, 5 days/week for 12 weeks. Guthion aerosols were generated by first dissolving technical-grade guthion in a 1:1 solution of ethanol/polypropylene glycol. Ninety-seven percent of the droplets had a diameter of 1±0.5 μm (Kimmerle 1976). The animals were inspected daily and weighed weekly. Erythrocyte AChE and plasma ChE activities were determined after 2, 4, 6, 8, 10, and 12 weeks and determinations of hematology, SGOT, SGPT, alkaline phosphatase, urea, creatinine, and bilirubin were conducted after 12 weeks of exposure. At study termination, animals were sacrificed for gross examination. The thyroid, thymus, heart, lungs, liver, spleen, kidneys, adrenals, and gonads were weighed and examined histologically and brain AChE activity was determined.

Effect noted in study and corresponding doses: There were no significant changes in appearance or behavior of male or female rats. Male rats in the 4.72 mg/m^3 group showed a 20% reduction in body weight gain during the 12-week exposure period. No effects were detected in the examined hematological and serum clinical chemistry parameters. There were no observed differences in absolute or relative organ weights or morphological alterations in organs or tissues in any of the rats. From week 4 to week 12, erythrocyte AChE activity was reduced by 29–48% in male and 26–39% in female rats in the 4.72 mg/m^3 group. Reductions in erythrocyte AChE activity in rats exposed to guthion doses <4.72 mg/m^3 were 17% or less and are not considered an adverse effect. The investigator noted that brain AChE activity was not reduced at any of the concentrations tested, but no data were shown.

Dose and end point used for MRL derivation: The MRL is based on a NOAEL of 1.24 mg/m^3 and LOAEL of 4.72 mg/m^3 for decreased erythrocyte AChE activity.

[X] NOAEL   [ ] LOAEL

Uncertainty Factors used in MRL derivation:

        [ ] 10 for use of a LOAEL
        [X]   3 for extrapolation from animals to humans
        [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

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If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The
NOAEL of 1.24 mg/m^3 was adjusted for intermittent exposure (NOAEL[ADJ]) as follows:

$$\text{NOAEL}_{[ADJ]} = 1.24 \text{ mg/m}^3 \text{ x 6 hours/24 hours x 5 days/7 days}$$
$$\text{NOAEL}_{[ADJ]} = 0.22 \text{ mg/m}^3$$

The human equivalent concentration (HEC) of the NOAEL[ADJ] was calculated using the equations below.
The RDDR[ER] is the regionally deposited dose ratio for the extrarespiratory effects. It is calculated using
EPA's software (version 2.3) for calculating RDDRs (EPA 1994b) and particle size and body weight data
from Kimmerle (1976).

$$\text{NOAEL}_{[HEC]} = \text{NOAEL}_{[ADJ]} \text{ x RDDR}_{[ER]}$$
$$\text{NOAEL}_{[HEC]} = 0.22 \text{ mg/m}^3 \text{ x 1.695}$$
$$\text{NOAEL}_{[HEC]} = 0.37 \text{ mg/m}^3$$

An RDDR$_{ER}$ of 1.695 was estimated using the default parameters and body weight data presented in
Table A-3.

Table A-3. Default Parameters Used in the Derivation of RDDR$_{ER}$

Parameter	Humans	Rats
Body weight (kg)	70.00	0.253[a]
Minute volume (L)	13.80	0.182
ET area (cm^2)[b]	200.00	15.00
TB area (cm^2)[c]	3,200.00	22.50
PU area (m^2)[d]	54.00	0.34

[a]12-week body weight value from Kimmerle (1976)
[b]Extrathoracic respiratory tract region
[c]Tracheobronchial respiratory tract region
[d]Pulmonary respiratory tract region

RDDR$_{ER}$ = regionally deposited dose ratio for the extrarespiratory effects

Based on the information provided by Kimmerle (1976), it was assumed that the sizes of the aerosol
particles were log-normally distributed in a manner such that 1.5% of these were <0.5 μm and 1.5% were
>1.5 μm. Based on these assumptions, a geometric mean and geometric standard deviation of 0.9 and
0.23 μm, respectively, were calculated. These values were used to calculate a MMAD of 0.88 μm using
the recommended equation in Table H-2 of the guidance document Methods for Derivation of Inhalation
Reference Concentrations and Application of Inhalation Dosimetry (EPA 1994b).

$$\text{MMAD} = \text{CMAD e}(3[\text{ln variance}]^2)$$

No conversion is required for the geometric standard deviation and the geometric standard deviation of
0.23 was used. CMAD is the count median aerodynamic diameter (0.9 μm).

The NOAEL$_{[HEC]}$ of 0.37 mg/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from
animals to humans using dosimetric adjustment and 10 for human variability), resulting in an
intermediate-duration inhalation MRL of 0.01 mg/m^3. Application of the benchmark dose methodology
to the data from Kimmerle (1976) was considered, but the data were presented as means without standard

errors or standard deviations. Without these measures, the benchmark dose methodology could not be applied.

Was a conversion used from intermittent to continuous exposure? Yes, animals were exposed 6 hours/day, 5 days/week.

$\text{NOAEL}_{[ADJ]} = 1.24 \text{ mg/m}^3 \text{ x 6 hours/24 hours x 5 days/7 days}$
$\text{NOAEL}_{[ADJ]} = 0.22 \text{ mg/m}^3$

Other additional studies or pertinent information that lend support to this MRL: No studies were located that allowed the derivation of a chronic-duration inhalation MRL. However, the available acute- and intermediate-duration inhalation studies and the acute-, intermediate-, and chronic-duration oral exposure studies support adopting the intermediate-duration MRL for chronic-duration exposures. Erythrocyte AChE activity was reduced by 29–48% in male rats and 26–39% in female rats exposed to guthion aerosols at 4.72 mg/m^3 for 4–12 weeks without evident biologically significant changes in activity within the observation period (Kimmerle 1976). Intermediate- and chronic-duration oral exposures to 0.69–0.78 mg/kg/day in dogs (Allen et al. 1990) and 0.75–0.96 mg/kg/day in rats (Schmidt and Chevalier 1984) demonstrated biologically significant reductions in erythrocyte AChE activity that did not increase in severity with increasing exposure duration for up to 2 years (Allen et al. 1990; Schmidt and Chevalier 1984). Thus, a chronic-duration inhalation MRL of 0.01 mg/m^3 is adopted from the intermediate-duration inhalation MRL and supported by the intermediate- and chronic-duration oral exposure studies in dogs and rats, which suggest that there are no duration-dependent increases in the severity of the inhibition of erythrocyte AChE activity.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation   [X] Oral
Duration: [X] Acute   [ ] Intermediate   [ ] Chronic
Graph Key: 11
Species: Rats

Minimal Risk Level: 0.01 [X] mg/kg/day   [ ] ppm

Reference: Astroff AB, Young AD. 1998. The relationship between maternal and fetal effects following maternal organophosphate exposure during gestation in the rat. Toxicol Ind Health 14(6):869-889.

Experimental design: Pregnant Sprague-Dawley rats were administered guthion (87.7% a.i.) at 0.5, 1.0, or 2.0 mg/kg/day by gavage on gestation days 6–15 (Astroff and Young 1998). Erythrocyte AChE was determined on gestation days 16 and 20 and brain AChE activity was determined on day 20. Inseminated females were examined daily for clinical signs. Dam body weight was determined on gestation days 0, 6, 8, 10, 12, 15, and 20. Food consumption was also determined periodically. Two groups of dams were used to establish maternal plasma ChE and erythrocyte and brain AChE activities on gestation days 16 and 20. Gross pathological examination of dams was conducted. Several reproductive and developmental end points, including early or late resorptions, implantation losses, and fetal survival, growth, and malformations were evaluated.

Effect noted in study and corresponding doses: A >80% reduction in erythrocyte AChE activity was observed 24 hours after the last 2.0 mg/kg/day dose. A 40% reduction in brain AChE activity was also observed in dams in the 2.0 mg/kg/day group. Maternal plasma ChE activity in the 2.0 mg/kg/day group was approximately 30% lower than in controls on gestation day 16, but the effect was not statistically significant. On gestation day 20, maternal brain AChE activity remained 27% lower than control values, but erythrocyte AChE and plasma ChE activities were not significantly different from those of control animals. In spite of the magnitude of the AChE and ChE activity reductions, there were no adverse clinical signs observed in the treated dams. There were no statistically or biologically significant reductions in brain or erythrocyte AChE or plasma ChE activities in rats administered 0.5 or 1 mg/kg/day.

Dose and end point used for MRL derivation: The MRL is based on a BMDL of 1.04 mg/kg/day for inhibition of erythrocyte AChE activity.

[ ] NOAEL   [ ] LOAEL   [X] BMDL

In order to derive a point of departure to calculate an acute-duration oral MRL, a benchmark dose approach was applied to the changes in erythrocyte AChE activity observed in female rats exposed to guthion by gavage during gestation. Benchmark doses (BMDs) and the lower bound of the 95% confidence limits of the benchmark doses (BMDLs) were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2) as described below. The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity.

The simplest continuous variable model (a linear model) did not provide an adequate fit to the erythrocyte AChE activity data. Thus, four continuous variable models were fit to the erythrocyte AChE activity data presented in Table A-4. Results of the modeling are presented in Table A-5.

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Table A-4. Erythrocyte Cholinesterase Activity in Female Rats Administered Guthion

Guthion dose (mg/kg/day)	Number of animals tested	Erythrocyte AChE activity (IU/mL)	Standard deviation	Percent inhibition
0	24	0.36	0.10	–
0.5	19	0.32	0.06	11
1.0	27	0.32	0.09	11
2.0	26	0.07	0.03	81

Source: Astroff and Young 1998

Table A-5. Model Predictions for Changes in Erythrocyte Cholinesterase Activity in Female Rats

Model	Variance p-value[a]	X^2 test statistic for means	df	p-Value for the means[a]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Linear[b]	<0.0001	29.9864	2	<0.0001	-369.520477	–	–
Linear[c]	0.1257	34.808	2	<0.0001	-390.935378	–	–
2-degree polynomial[d]	0.1257	5.50139	1	0.019	-418.242024	–	–
Power[c,e]	0.1257	3.42361	1	0.06427	-420.319802	1.32753	1.03839
Hill[f]	0.1257	3.42499	0	NA	-418.318425	–	–

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Best-fitting model
[d]The lowest degree polynomial providing an adequate fit is reported
[e]Restrict power >=1
[f]Restrict n>1

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; df = degree of freedom; NA = not available (BMD software could not generate a model output); p = p-value from the chi-squared test

An adequate fit to the data for changes in erythrocyte AChE activity (as assessed by chi-square residuals and log-likelihood ratio fit tests in the BMDS) was obtained only with the power model with nonconstant variance assumed. A limitation of this data set is the large difference in maternal erythrocyte AChE activity between the NOAEL and the next, higher dose; relative to controls, maternal erythrocyte AChE activity was 11% lower in the 1 mg/kg/day group and 81% lower in the 2 mg/kg/day group. Statistical tests indicated that variances were not constant across exposure groups. The power model with non-homogeneous variance (i.e., variance as a power function of dose) provided an improved fit to the data as assessed with Akaike's Information Criteria (AIC) (Table A-5). The BMD and BMDL predicted from the power model are 1.33 and 1.04 mg/kg/day, respectively (Table A-5 and Figure A-1).

APPENDIX A

Figure A-1. Model Predictions for Changes in Erythrocyte Cholinesterase Activity in Female Rats
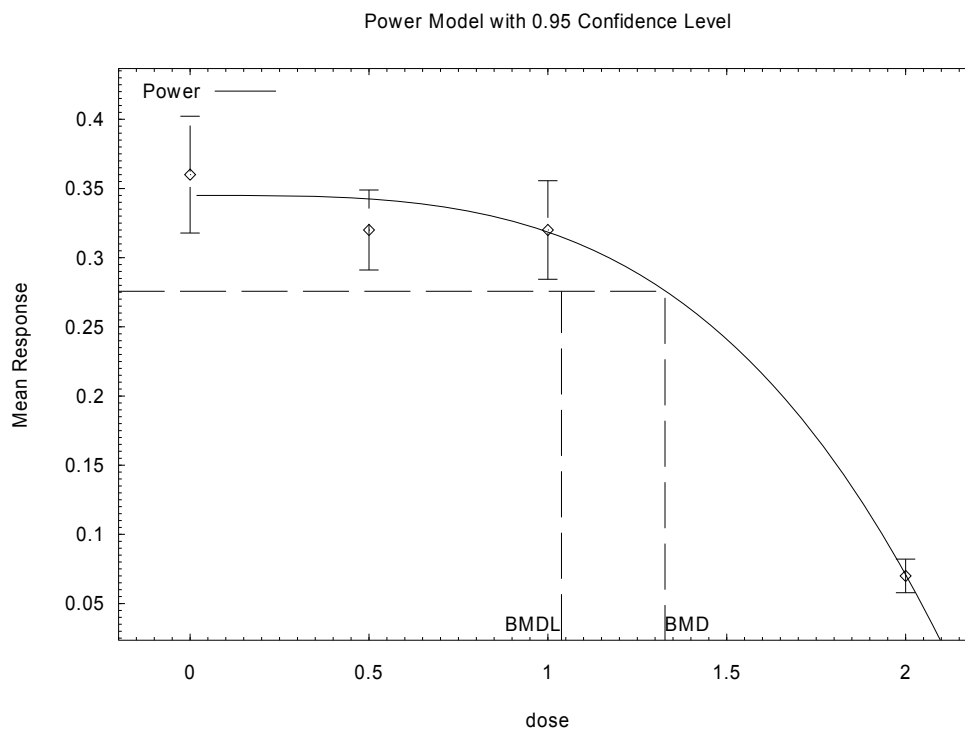
Power Model with 0.95 Confidence Level

14:23 04/04 2006

Uncertainty Factors used in MRL derivation:

    [ ] 10 for use of a LOAEL
    [X] 10 for extrapolation from animals to humans
    [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Pasquet et al. (1976) observed reductions in erythrocyte and brain AChE activity in rats after single oral doses of guthion at 2, 6, or 18 mg/kg. Plasma ChE activity was reduced by ≥20% at >2 mg/kg, while brain AChE activity was reduced by ≥20% at doses ≥2 mg/kg/day. The results of the BMD approach is supported by the observation that application of a NOAEL approach (NOAEL ÷ 100 [uncertainty factor] would result in an MRL equal to the BMDL ÷ 100 [uncertainty factor].

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation   [X] Oral
Duration: [ ] Acute   [X] Intermediate   [ ] Chronic
Graph Key: 40
Species: Dog

Minimal Risk Level: 0.003 [X] mg/kg/day   [ ] ppm

Reference: Allen TR, Janiak T, Frei T, et al. 1990. 52-Week oral toxicity (feeding) study with azinphos-methyl (E 1582) in the dog. Mobay Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41804801.

Experimental design: Technical-grade guthion (91.9% a.i.) was administered to beagle dogs (four dogs/sex/group) in the food at 5.0, 25.0, and 125.0 ppm for up to 52 weeks. The guthion concentrations are equivalent to 0.15, 0.69, and 3.8 mg/kg/day, respectively, in male dogs, and 0.16, 0.78, and 4.3 mg/kg/day, respectively, in female dogs (Allen et al. 1990). The observations made at ≤26 weeks were used to derive the intermediate-duration MRL. Daily observations for clinical signs were conducted; body weight was determined weekly and food consumption was monitored daily. Hearing and ophthalmoscopic evaluations were conducted after 13, 26, and 52 weeks; hematological, clinical chemistry, and urinary chemistry parameters were determined on weeks 4, 13, 26, and 52; plasma ChE and erythrocyte AChE activities were determined on weeks 4, 13, and 26.

Effect noted in study and corresponding doses: Reductions of ≥20% in erythrocyte AChE activity were observed after 4, 13, and 26 weeks in male and female dogs administered guthion in food for up to 52 weeks (Allen et al. 1990). Dose-related reductions in erythrocyte AChE activity were evident at the week 4 sampling time. Erythrocyte AChE activity was further reduced from week 4 to week 13 but remained relatively constant from week 13 to 26 (Allen et al. 1990). Statistically nonsignificant reductions in erythrocyte AChE activity during the 26-week period were ≤8% in males at 0.15 mg/kg/day and 11–21% in females at 0.16 mg/kg/day. Reductions in erythrocyte AChE activity were 22–40% in males at 0.69 mg/kg/day and 20–43% in females at 0.78 mg/kg/day. Reductions in erythrocyte AChE activity from weeks 4 to 26 were 66–88% in males (3.8 mg/kg/day) and 86–92% in females (4.3 mg/kg/day). The relatively constant levels of erythrocyte AChE activity from weeks 4 to 26 suggest that the effects of guthion on AChE activity occur early and remain relatively steady during exposure. Male and female dogs administered 3.8 and 4.3 mg/kg/day, respectively, suffered from an increased incidence of mucoid diarrhea and occasional emesis. The same signs but with a greater severity were observed in male dogs at 0.69 mg/kg/day. These signs were believed to be related to guthion treatment. Terminal body weights were reduced by 12–16% in male and female dogs administered 3.8 and 4.3 mg/kg/day, respectively, although there was no difference in food consumption among treated and control animals. There were no treatment-related hematological effects or changes in urinalysis parameters. Findings were negative in hearing and ophthalmoscopic tests on weeks 13 and 26 and there was no treatment-related increase in mortality in any dose group (Allen et al. 1990). Clinical chemistry tests showed that albumin and albumin/globulin values were significantly reduced in males by 13 and 20%, respectively, in the 3.8 mg/kg/day group.

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Dose and end point used for MRL derivation: The MRL is based on a BMDL of 0.29 mg/kg/day for inhibition of erythrocyte AChE activity in female dogs after 26 weeks.

[ ] NOAEL   [ ] LOAEL   [X] BMDL

In order to derive a point of departure to calculate an intermediate-duration oral MRL, a benchmark dose approach was applied to the changes in erythrocyte AChE activity observed in male and female dogs exposed to guthion in the diet for 26 weeks (Allen et al. 1990). It is recognized that the small number of animals per dose group (4 dogs/group) limits the characterization of variability in the response to guthion. Benchmark doses (BMDs) and the lower bound of the 95% confidence limits of the benchmark doses (BMDLs) were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2) as described below. The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity. The simplest continuous variable model (a linear model) was fit to the erythrocyte AChE activity data presented in Table A-6.

Table A-6. Erythrocyte Cholinesterase Activity (µmol/mL/minute) in Beagle Dogs Administered Guthion in the Diet for 26 Weeks (Four Dogs/Sex/Dose Group)

Dose (mg/kg/day)	Mean (standard deviation)	Percent reduction
Males		
0	2.57 (0.29)	–
0.15	2.37 (0.83)	8
0.69	1.75 (0.21)	32
3.8	0.32 (0.13)	88[a]
Females		
0	3.27 (0.38)	–
0.16	2.57 (0.63)	21
0.78	2.03 (0.53)	37[a]
4.3	0.28 (0.11)	91[a]

[a]Statistically significant reduction

Source: Allen et al. 1990

A nonhomogeneous variance linear model provided an adequate fit to the erythrocyte AChE activity data for female but not male dogs after 26–week and it was concluded that the male data at 26 weeks were not suitable for BMD modeling. For the 26-week data in female dogs, the best-fitting linear model predicted a BMD of 0.96 mg/kg/day and a BMDL of 0.93 mg/kg/day. However, this BMDL for a 20% reduction in erythrocyte AChE activity in dogs is higher than the observed LOAELs of 0.69 and 0.78 mg/kg/day in male and female dogs, respectively (Allen et al. 1990). At these LOAELs, reductions in erythrocyte AChE activity in the range of 32–37% were observed after 26 weeks. Thus, the linear model appears to underpredict the response of erythrocyte AChE activity to guthion in female dogs after 26 weeks. Reexamination of the data plots suggests that the experimental data at the high dose might be a high-leverage point, which exerts a high degree of influence on the model results. The plot of the erythrocyte AChE activity in female dogs after 26 weeks is presented in Figure A-2. Given that for the derivation of an MRL the most pertinent part of the dose-response curve is that which lies at the lower doses, the high-dose data point was removed from the dataset and the model fitting was conducted as described before. A nonhomogeneous variance linear model provided an adequate fit to the erythrocyte AChE activity data for females at week 26 when the high dose was removed from the data set. None of the other continuous

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models available in the BMD software provided an adequate fit to the data. Results of the BMD linear modeling of the low-dose region of the dose-response curve are presented in Table A-7 and a plot of the 26-week data in females with the high-dose excluded is presented in Figure A-3.

Table A-7. Model Predictions for Erythrocyte AChE Activity in Female Beagle Dogs Exposed to Guthion in the Diet for 26 Weeks

Model	Variance p-value[a]	X^2 test statistic for means	df	p-value for the means[a]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Linear[b,c,d] (high dose excluded)	0.43	2.47	1	0.12	3.12	0.44	0.29

[a]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Best-fitting model
[d]Restriction = nonpositive

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; df = degree of freedom; p = p value from the Chi-squared test
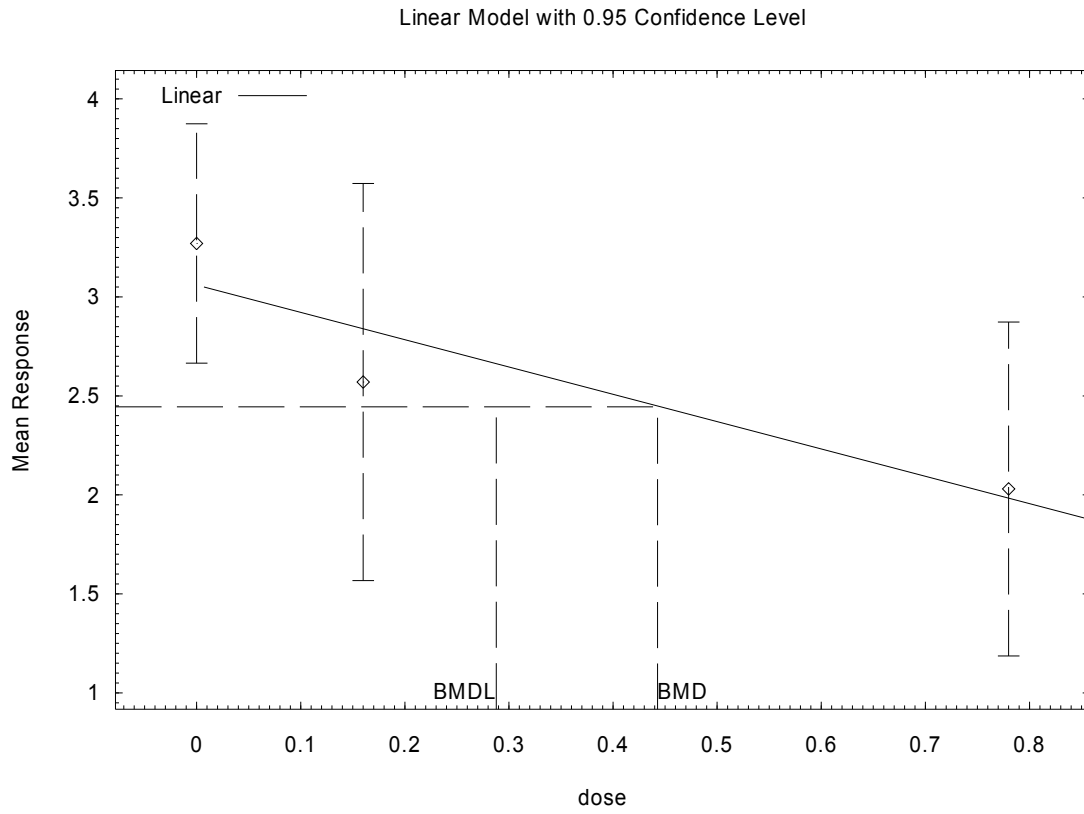
APPENDIX A

Figure A-2. Erythrocyte AChE Activity in Female Beagle Dogs Exposed to Guthion in the Diet for 26 Weeks*(Complete Dataset)

Linear Model with 0.95 Confidence Level
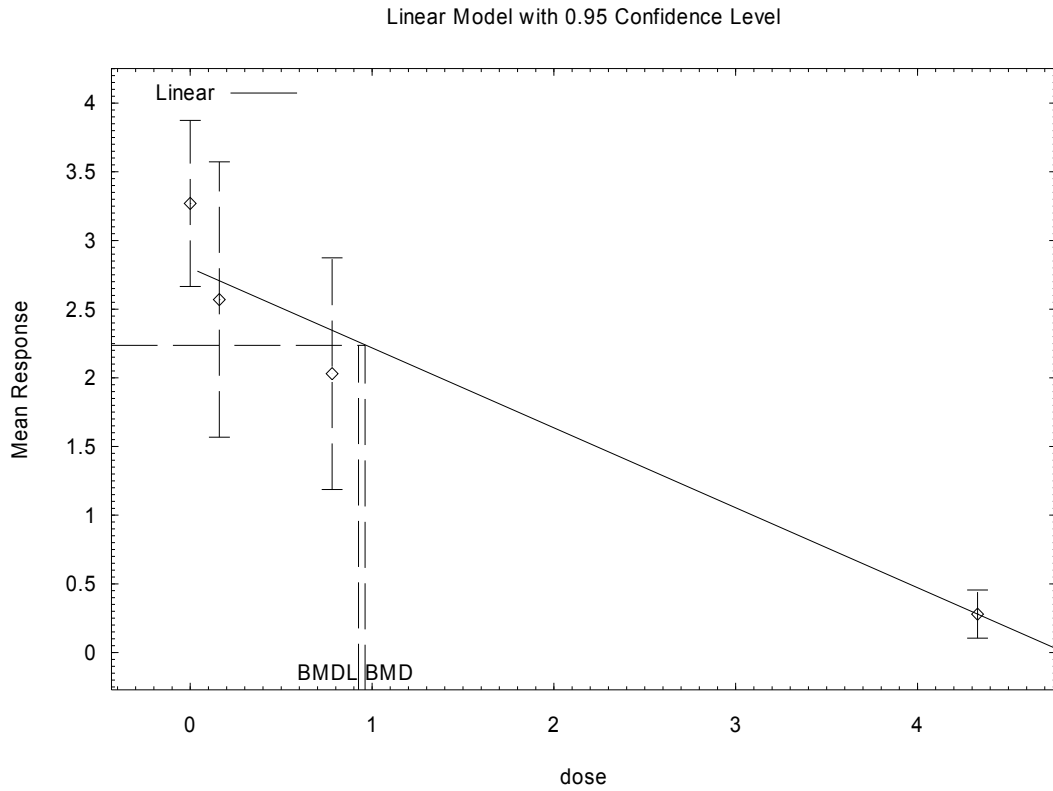
14:14 04/20 2006

*BMDs and BMDLs are associated with a 20% change from the controls, and are in units of mg/kg/day.

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Figure A-3. Erythrocyte AChE Activity in Female Beagle Dogs Exposed to Guthion in the Diet for 26 Weeks* (High-dose Group Excluded)

Linear Model with 0.95 Confidence Level

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*BMDs and BMDLs indicated are associated with a change of 20% change from the control, and are in units of mg/kg/day

A BMDL of 0.29 mg/kg/day was obtained by analysis of the low-dose region of the dose-response curve for dogs exposed for 26 weeks.

Uncertainty Factors used in MRL derivation:

       [ ] 10 for use of a LOAEL
       [X] 10 for extrapolation from animals to humans
       [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Inhibition of erythrocyte AChE activity was the most sensitive end point in a study with male and female rats administered technical-grade guthion in the feed for 13 weeks (Sheets et al. 1997). Brain and erythrocyte AChE activities were significantly inhibited in rats administered ≥0.91 mg/kg/day. The results obtained using the BMD approach are supported by those obtained using the NOAEL approach.

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Guthion
CAS Numbers: 86-50-0
Date: June 2008
Profile Status: Final Draft Post-Public Comment
Route: [ ] Inhalation   [X] Oral
Duration: [ ] Acute   [ ] Intermediate   [X] Chronic
Graph Key: 63
Species: Dog

Minimal Risk Level: 0.003 [X] mg/kg/day   [ ] ppm

Reference: Allen TR, Janiak T, Frei T, et al. 1990. 52-Week oral toxicity (feeding) study with azinphos-methyl (E 1582) in the dog. Mobay Corporation. Submitted to the U.S. Environmental Protection Agency. MRID41804801.

Experimental design: Technical-grade guthion (91.9% a.i.) was administered to beagle dogs (four dogs/sex/group) in the food at 5.0, 25.0, 125.0 ppm for up to 52 weeks. The guthion concentrations are equivalent to 0.15, 0.69, and 3.8 mg/kg/day, respectively, in male dogs, and 0.16, 0.78, and 4.3 mg/kg/day, respectively, in female dogs (Allen et al. 1990). Daily observations for clinical signs were conducted; body weight was determined weekly and food consumption was monitored daily. Hearing and ophthalmoscopic evaluations were conducted after 13, 26, and 52 weeks; hematological, clinical chemistry, and urinary chemistry parameters were determined on weeks 4, 13, 26, and 52; plasma ChE and erythrocyte AChE activities were determined prior to treatment and on weeks 4, 13, 26, and 52; brain AChE activity was determined on week 52. Terminal body weight and organ weights were determined and macroscopic and histopathological evaluations of organs were conducted.

Effect noted in study and corresponding doses: Dose-related reductions in erythrocyte AChE activity were evident in male and female dogs on week 52. A statistically nonsignificant reduction of 15% in erythrocyte AChE activity was observed in females at 0.16 mg/kg/day on week 52, but there was no effect in males. On week 52, reductions in erythrocyte AChE activity in males at 0.69 and 3.8 mg/kg/day were 27 and 86%, respectively. Females in the 0.78 and 4.3 mg/kg/day groups showed 35 and 86% reductions, respectively, in erythrocyte AChE activity. Brain AChE activity on week 52 in the 3.8 and 4.3 mg/kg/day groups was reduced by 27 and 20% in males and females, respectively. Reductions in brain AChE activity were 1 and 10% in female and male dogs receiving administered 0.78 and 0.69 mg/kg/day, respectively. No effect on brain AChE activity was observed in males administered 0.15 mg/kg/day or females administered 0.16 mg/kg/day. Plasma ChE activity was reduced by 53% in males and females administered 3.8 and 4.3 mg/kg/day, respectively. No statistically significant reductions in plasma ChE activity were observed in male or female dogs administered ≤0.69 or ≤0.78 mg/kg/day, respectively. Terminal body weights were reduced by 12% in males in the 3.8 mg/kg/day group and by 16% in females in the 4.3 mg/kg/day group, although there was no difference in food consumption among treated and control animals. There were no treatment-related hematological effects or changes in urinalysis parameters. Findings were negative in hearing and ophthalmoscopic tests conducted at study termination and there was no treatment-related increase in mortality in any dose group. There were no changes in absolute or relative organ weights in females at the doses tested. Absolute and relative spleen weights in were reduced in males in a dose-related manner with significant reductions in relative spleen weight at ≥0.69 mg/kg/day; however, congestion of the spleen and increased absolute spleen weight were observed in 4/4 male dogs in the control group. A 7–17% decrease in albumin and albumin/globulin values were observed on week 52 in males in the 3.8 mg/kg/day group. A 39 and 15% increase in P450 activity was observed in male dogs at 3.8 mg/kg/day and in female dogs at

4.3 mg/kg/day, respectively. A 34 and 30% increase in N-demethylase activity was observed in male dogs at 3.8 and in female dogs at 4.3 mg/kg/day, respectively. Other effects were restricted to the high dose groups (Allen et al. 1990).

Dose and end point used for MRL derivation: The MRL is based on a BMDL of 0.30 mg/kg/day for inhibition of erythrocyte AChE activity in male dogs after 52 weeks.

[ ] NOAEL [ ] LOAEL [X] BMDL

In order to derive a point of departure to calculate a chronic-duration oral MRL a benchmark dose approach was applied to the changes in erythrocyte AChE activity observed in male and female dogs exposed to guthion in the diet for 52 weeks (Allen et al. 1990). It is recognized that the small number of animals per dose group (4 dogs/group) limits the characterization of variability in the response to guthion. Benchmark doses (BMDs) and the lower bound of the 95% confidence limits of the benchmark doses (BMDLs) were calculated using the EPA Benchmark Dose Software (BMDS version 1.3.2) as described below. The BMDs and BMDLs are estimates of the doses associated with a 20% change in erythrocyte AChE activity. The simplest continuous variable model (a linear model) was fit to the erythrocyte AChE activity data presented in Table A-8.

Table A-8. Erythrocyte Cholinesterase Activity (µmol/mL/minute) in Beagle Dogs Administered Guthion in the Diet for 52 Weeks (Four Dogs/Sex/Dose Group)

Dose (mg/kg/day)	Mean (standard deviation)	Percent reduction
Males		
0	2.87 (0.36)	–
0.15	3.01 (0.84)	0
0.69	2.10 (0.45)	27
3.8	0.41 (0.15)	86[a]
Females		
0	3.36 (1.72)	–
0.16	2.87 (0.73)	15
0.78	2.20 (0.5)	35[a]
4.3	0.47 (0.16)	86[a]

[a]Statistically significant reduction

Source: Allen et al. 1990

The linear model under the assumption of constant variance did not provide an adequate fit for either the male or female erythrocyte AChE activity data at 52 weeks; however, a nonhomogeneous variance linear model provided an adequate fit to the erythrocyte AChE activity data for males and females at week 52. Therefore, the linear model with the assumption of nonhomogenous variance was chosen for estimating the BMDs and BMDLs for the males and females at week 52. The selected model predicted a BMD in the range of 0.90–1.0 mg/kg/day and a BMDL in the range of 0.85–0.97 mg/kg/day. However, these BMDLs for a 20% reduction in erythrocyte AChE activity in dogs are higher than the observed LOAELs of 0.69 and 0.78 mg/kg/day in male and female dogs, respectively (Allen et al. 1990). At these LOAELs, reductions in erythrocyte AChE activity in the range of 27–35% were observed after 52 weeks. Thus, the linear model appears to underpredict the response of erythrocyte AChE activity to guthion in dogs after

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52 weeks. Reexamination of the data plots suggests that the experimental data at the high dose might be a high-leverage point which exerts a high degree of influence on the model results. The plots of the erythrocyte AChE activity in male and female dogs after 52 weeks are presented in Figures A-4(A) and A-5(A), respectively. Given that for the derivation of an MRL the most pertinent part of the dose-response curve is that which lies at the lower doses the high-dose data point was removed from the dataset and the model fitting was conducted as described before. A linear model with an assumption of homogenous variance provided an adequate fit to the 52-week data with dogs when the high-dose data were removed. The other continuous models in the software were also applied to the data, but did not provide adequate fits. Results of the BMD linear modeling of the low-dose region of the dose-response curve are presented in Table A-9. Plots of the 52-week data in males and females with the high-dose excluded are presented in Figures A-4(B) and A-5(B), respectively.

Table A-9. Model Predictions for Erythrocyte AChE Activity in Beagle Dogs Exposed to Guthion in the Diet for 52 Weeks

Model	Variance p-value[a]	X^2 test statistic for means	df	p-value for the means[a]	AIC	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male							
Linear[b,c] (high dose dropped)	0.20	0.85	1	0.36	0.66	0.48	0.30
Female							
Linear[b,c] (high dose dropped)	0.55	1.5	1	0.23	14.5	0.50	0.32

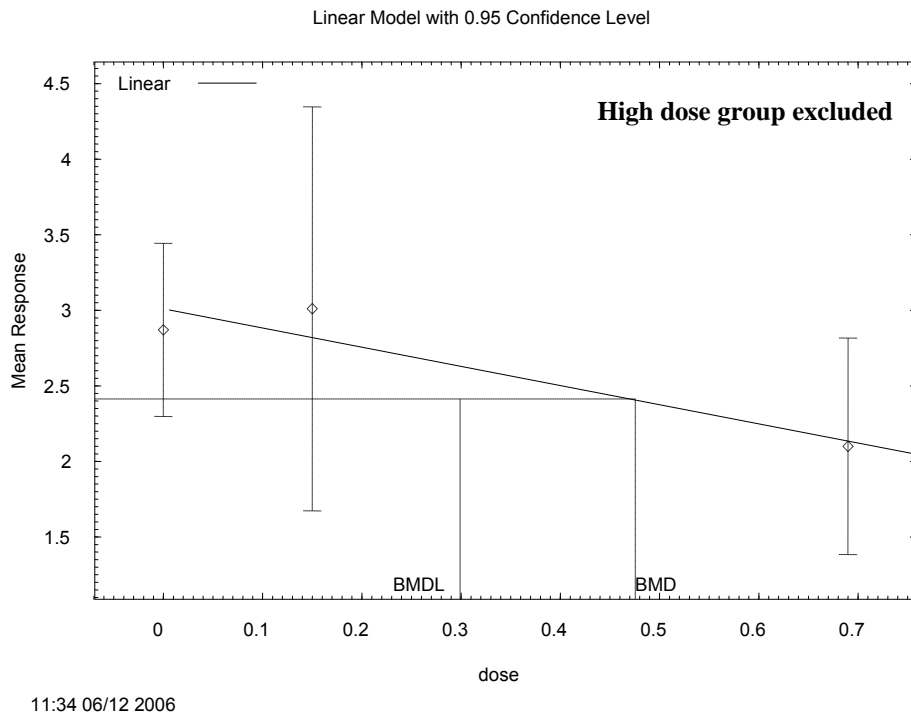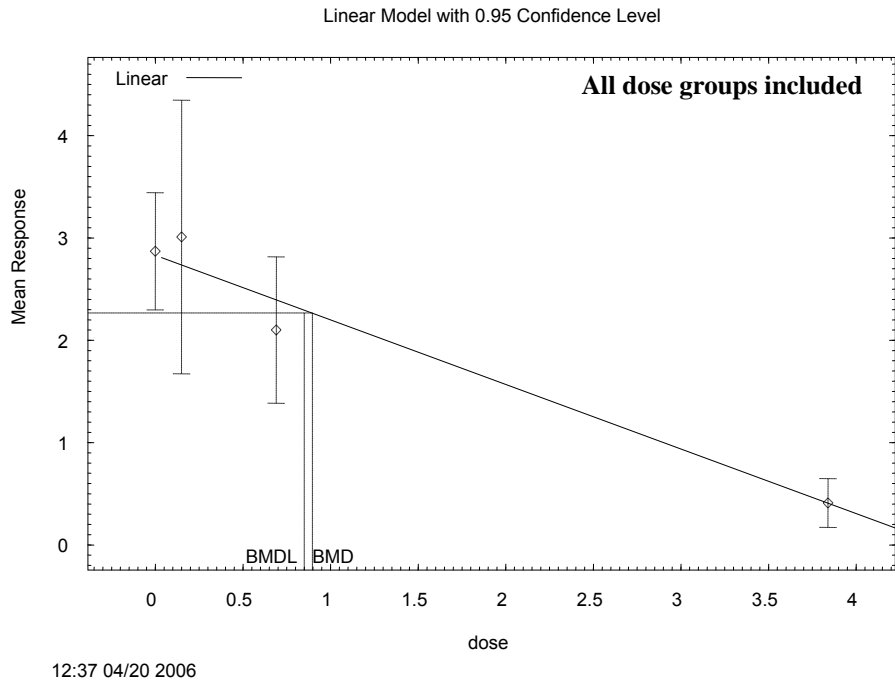[a]Values <0.05 fail to meet conventional goodness-of-fit criteria.
[b]Constant variance assumed
[c]Restriction = nonpositive

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; df = degree of freedom; p = p value from the Chi-squared test
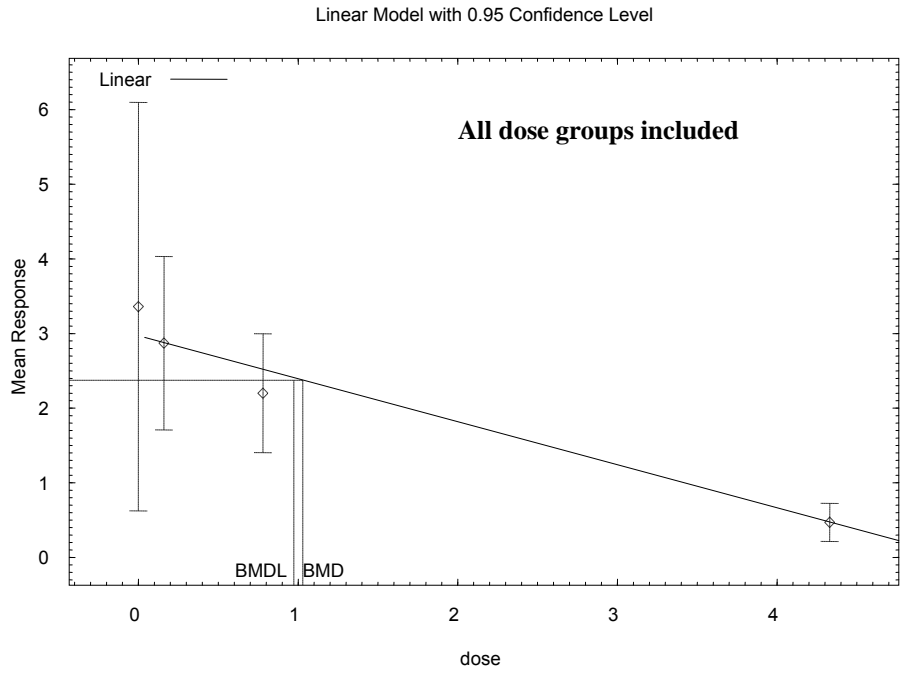
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Figure A-4. Erythrocyte AChE Activity in Male Beagle Dogs Exposed to Guthion in the Diet for 52 Weeks*

Linear Model with 0.95 Confidence Level

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Linear Model with 0.95 Confidence Level
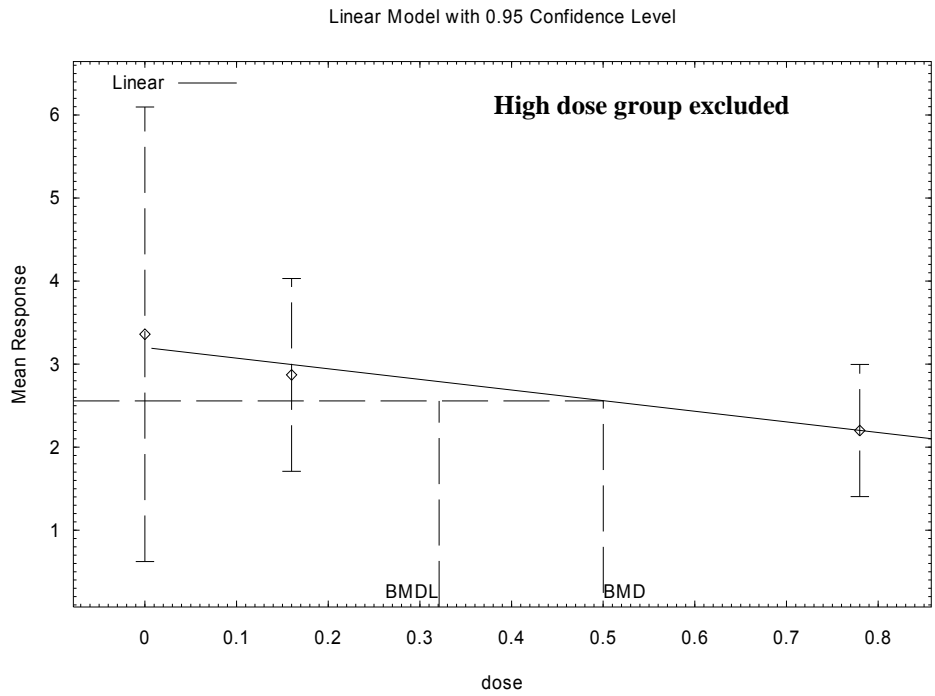

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*BMDs and BMDLs are associated with a 20% change from the controls, and are in units of mg/kg/day.

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Figure A-5. Erythrocyte AChE Activity in Female Beagle Dogs
Exposed to Guthion in the Diet for 52 Weeks*

Linear Model with 0.95 Confidence Level

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Linear Model with 0.95 Confidence Level

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*BMDs and BMDLs are associated with a 20% change from controls, and are in units of mg/kg/day.

APPENDIX A

BMDLs of in the range of 0.30–0.32 mg/kg/day were obtained by analysis of the low-dose region only of the dose-response curve for dogs exposed for 52 weeks. The lowest BMDL (0.30 mg/kg/day) was selected as the point of departure. Applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to the BMDL yields a chronic-duration oral MRL of 0.003 mg/kg/day.

Uncertainty Factors used in MRL derivation:

       [ ] 10 for use of a LOAEL
       [X] 10 for extrapolation from animals to humans
       [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Inhibition of erythrocyte AChE activity also was the most sensitive effect in a 2-year study with rats administered guthion in the diet at 0.25–2.3 mg/kg/day in males and 0.31–3.11 mg/kg/day in females (Schmidt and Chevalier 1984). These studies support selection of the effect on erythrocyte AChE activity as the critical end point for chronic oral exposure to azinphos-methyl. The 52-week study in dogs (Allen et al. 1990) was selected to derive the chronic-duration oral MRL because, at similar doses (0.69–0.78 mg/kg/day in dogs after 52 weeks and 0.75–0.96 mg/kg/day in rats after 2 years), there was a more marked reduction in erythrocyte AChE in dogs (20–43%) than in rats (10–22%).

Agency Contacts (Chemical Managers): Nickolette Roney, Selene Chou, Yee-Wan Stevens

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

APPENDIX B

LEGEND
See Sample LSE Table 3-1 (page B-6)

(1)   Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2)   Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15– 364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3)   Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4)   Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5)   Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6)   Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7)   System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8)   NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9)   LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect.
        LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help
        readers identify the levels of exposure at which adverse health effects first appear and the
        gradation of effects with increasing dose. A brief description of the specific end point used to
        quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key
        number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from
        Serious LOAELs.

(10)   Reference. The complete reference citation is given in Chapter 9 of the profile.

(11)   CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in
        experimental or epidemiologic studies. CELs are always considered serious effects. The LSE
        tables and figures do not contain NOAELs for cancer, but the text may report doses not causing
        measurable cancer increases.

(12)   Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found
        in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to
        derive an MRL of 0.005 ppm.

LEGEND
See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the
reader quickly compare health effects according to exposure concentrations for particular exposure
periods.

(13)   Exposure Period. The same exposure periods appear as in the LSE table. In this example, health
        effects observed within the acute and intermediate exposure periods are illustrated.

(14)   Health Effect. These are the categories of health effects for which reliable quantitative data
        exists. The same health effects appear in the LSE table.

(15)   Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are
        graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log
        scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in
        mg/kg/day.

(16)   NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in
        the rat upon which an intermediate inhalation exposure MRL is based. The key number 18
        corresponds to the entry in the LSE table. The dashed descending arrow indicates the
        extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of
        0.005 ppm (see footnote "b" in the LSE table).

(17)   CEL. Key number 38m is one of three studies for which CELs were derived. The diamond
        symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the
        LSE table.

APPENDIX B

(18)   <u>Estimated Upper-Bound Human Cancer Risk Levels</u>. This is the range associated with the upper-
        bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived
        from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the
        cancer dose response curve at low dose levels (q_1*).

(19)   <u>Key to LSE Figure</u>. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

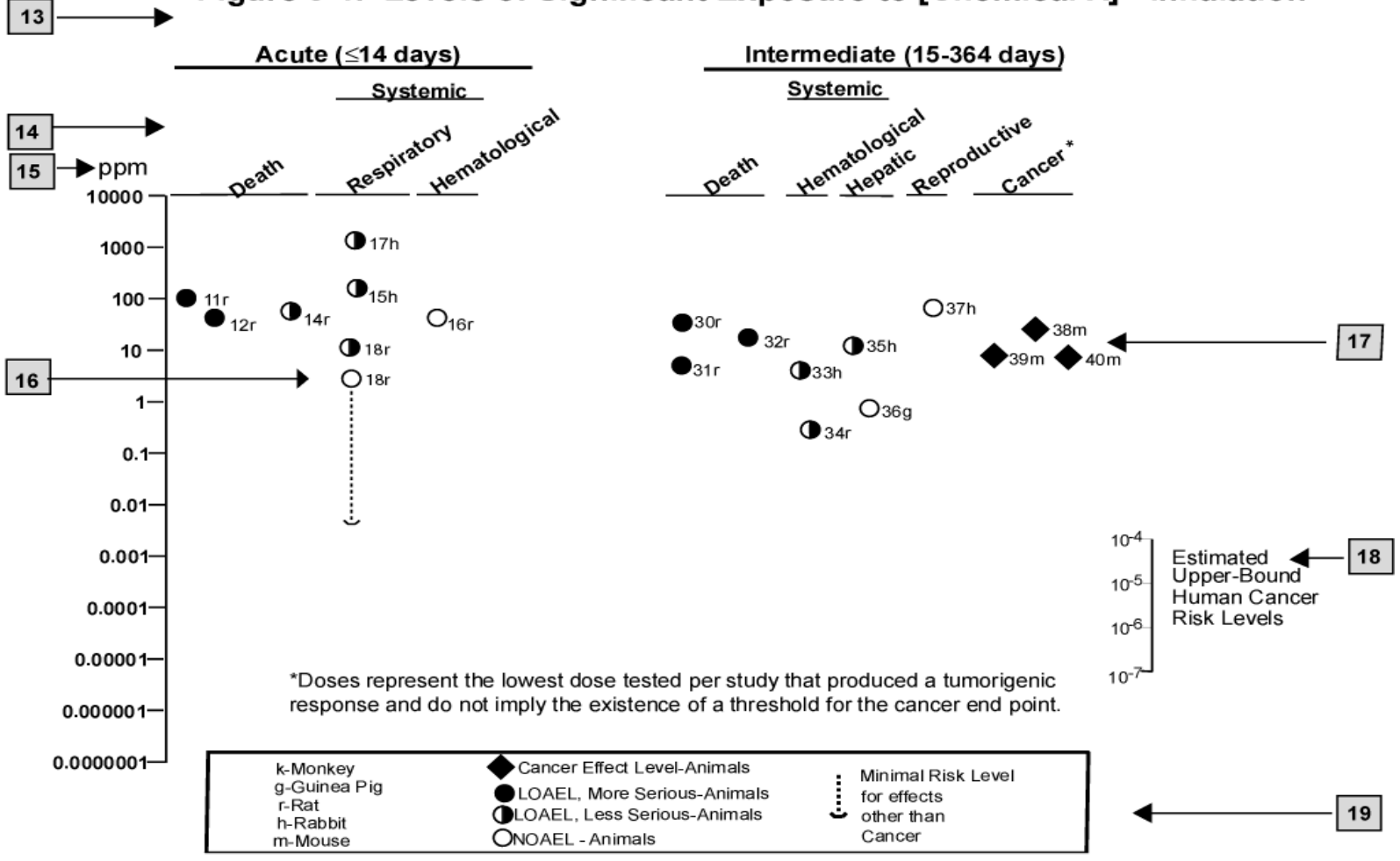## Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

1 →

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 →

[a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

Estimated Upper-Bound Human Cancer Risk Levels

k-Monkey
g-Guinea Pig
r-Rat
h-Rabbit
m-Mouse

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◐ LOAEL, Less Serious-Animals
○ NOAEL - Animals

Minimal Risk Level for effects other than Cancer

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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/Intergovernmental Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

APPENDIX C

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

APPENDIX C

PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

APPENDIX C

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
−	negative
+	positive
(+)	weakly positive result
(−)	weakly negative result

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APPENDIX D. INDEX

APPENDIX D