U.S. Army Center for Health Promotion and Preventive Medicine

USACHPPM

Wildlife Toxicity Assessment for Thiodiglycol

OCTOBER 2008

Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program

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Readiness Thru Health

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Table of Contents

1. INTRODUCTION 1
2. TOXICITY PROFILE 2
   2.1 Literature Review 2
   2.2 Environmental Fate and Transport 2
   2.3 Summary of Mammalian Toxicology 3
      2.3.1 Mammalian Oral Toxicity 3
         2.3.1.1 Mammalian Oral Toxicity – Acute 3
         2.3.1.2 Mammalian Oral Toxicity – Subacute 3
         2.3.1.3 Mammalian Toxicity – Subchronic 4
         2.3.1.3 Mammalian Toxicity – Chronic 4
         2.3.1.5 Mammalian Toxicity - Other 4
      2.3.1.6 Studies Relevant for Mammalian TRV Development for Ingestion Exposures 6
      2.3.2 Mammalian Toxicity- Inhalation 9
      2.3.3 Mammalian Toxicity- Dermal 9
   2.4 Summary of Avian Toxicology 9
   2.5 Summary of Amphibian Toxicology 9
   2.6 Summary of Reptilian Toxicology 9
3. RECOMMENDED TOXICITY REFERENCE VALUES 10
   3.1 Toxicity Reference Values for Mammals 10
      3.1.1 TRVs for Ingestion Exposures for the Class Mammalia 10
      3.1.2 TRVs for Ingestion Exposures for Mammalian Foraging Guilds 11
      3.1.3 TRVs for Inhalation Exposures for the Class Mammalia 11
      3.1.4 TRVs for Dermal Exposures for the Class Mammalia 11
   3.2 Toxicity Reference Values for Birds 12
   3.3 Toxicity Reference Values for Amphibians 12
   3.4 Toxicity Reference Values for Reptiles 12
4. IMPORTANT RESEARCH NEEDS 12
5. REFERENCES 13

APPENDIX A – LITERATURE REVIEW A-1

Department of the Army

U.S. Army Center for Health Promotion and Preventive Medicine

Wildlife Toxicity Assessment for Thiodiglycol

CAS No. 111-48-8 **October 2008**

1. INTRODUCTION

Thiodiglycol (TDG) is an oily liquid that is used commercially as a solvent in antifreeze solutions, dyestuffs for printing, and as part of the process by which polyvinyl chloride is manufactured (Munro et al. 1999). The compound is also formed when the chemical warfare agent sulfur mustard (HD) undergoes hydrolysis. Thus, TDG has been detected in animals and human beings exposed to HD, and in environmental media when HD is released to the environment. Renewed interest in the environmental and human health impacts of TDG has arisen with the alleged use of HD by the military forces of Iraq against Iranians and their own Kurdish population during the 1980s (Wils et al., 1985, 1988). Of interest is (1) the extent to which the appearance of TDG in blood or urine can be taken as an indication that the subject was a victim of an HD attack, and (2) whether the existence of TDG in environmental media is itself a threat to wildlife.

There is limited information on the toxicity and environmental fate of TDG (Reddy et al., 2005). Thus, there are no records for TDG in the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System database or in the National Library of Medicine's Hazardous Substances Databank because of limited information on the toxicity and environmental fate of TDG (Reddy et al., 2005). No occupational standards or guidelines have been set for this compound by the National Institute of Occupational Safety and Health, the Occupational Safety and Health Administration, or the American Conference of Governmental Industrial Hygienists.

This Wildlife Toxicity Assessment summarizes the limited available information on the likely effects of TDG on wildlife, stressing where possible threshold doses for the onset of non-cancer effects, as described in reports of experimental studies of the compound. Surveying the threshold dosimetry of TDG may point to the establishment of toxicity reference values (TRVs) that could serve as protective exposure standards for all wildlife ranging in the vicinity of affected sites. The protocol for the performance of this

assessment is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. TOXICITY PROFILE

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were searched electronically on May 23, 2002, using DIALOG to identify primary reports of studies and reviews on the toxicology of TDG. A single search for TDG with no limiting descriptors yielded 291 hits that were evaluated initially in key-words-in-context. All articles selected in this Tier 1 evaluation as possibly relevant to TRV development were reevaluated as abstracts (Tier 2), then, if relevant, retrieved from local libraries or vendors. For TDG, 15 articles from the 291 initial hits were marked for retrieval. Details of the search strategy and its results are documented in Appendix A. Secondary references and sources of information on TDG included Merck Index (12th Edition) (Budavari et al. 1996), the 8th Edition of *Sax's Dangerous Properties of Industrial Materials* (Lewis 1992), and on-line information posted by the University of Oxford's Physical and Theoretical Chemistry Laboratory (UO 2002).

2.2 Environmental Fate and Transport

Few data were found on the fate and transport of TDG in the environment, although some characteristics can be inferred from the compound's physical-chemical properties (Table 1). For example, the miscibility of TDG in water suggests that the compound will readily partition to or be dispersed in aqueous media. The compound appears to be largely resistant to hydrolysis or photolysis (Munro et al. 1999). In a recent study using photoactivated periodate to decompose total organic carbon (TOC) from hydrolysates of chemical warfare agents, TDG had the fastest rate of TOC loss at pH 3 (Tang et al. 2008). Lee and Allen (1988) studied the environmental fate of TDG. They showed that its sorption to soils is less than 10 mg/kg, while its degradation product thiodiglycolic acid showed sorption capacity from 19.9 to 427 mg/kg, depending on soil type. They also found TDG and thiodiglycolic acid resistant to photolysis and hydrolysis. TDG is biologically converted to the latter with the formation of an intermediate [(2-hydroxyethyl)thio]acetic acid. TDG was slowly biodegraded under anaerobic conditions, reaching about 42 percent of applied dose after 185 days (Sklyar et al. 1999). An aerial application of TDG at 1 lb per acre on several crops showed no effect on the plants (Wiswesser and Frank et al. 1975, cited in Rosenblatt et al. 1975). Microbial degradation of TDG has been demonstrated in the presence of strains of *Pseudomonas pickettii* and *Alcaligenes xylosoxidans*, both of which are capable of growing in media with TDG as the sole carbon source (Ermakova et al., 2001). In addition, bioreactor experiments have demonstrated degradation of the compound in the presence of sewage sludge (Munro et

al., 1999).

Table 1. Summary of Physical-chemical Properties of Thiodiglycol

CAS No.	111-48-8
Molecular weight	122.2
Color	colorless
Physical state	syrupy liquid
Melting point	-10 ^{o}C
Boiling point	282 ^{o}C
Odor	ND
Solubility in water	miscible with water; soluble in chloroform
Partition coefficients:	
Log K_{ow}	-0.77
Log K_{oc}	0.99
Vapor pressure	2×10^{-5} mm Hg
Henry's Law constant at 25 ^{o}C	ND
Conversion factors	1 ppm = 5 mg/m^3
	1 mg/m^3 = 0.2 ppm

Sources: Lewis (1992) ; Budavari et al. (1996); UO (2002); Munro et al. (1999);

2.3 Summary of Mammalian Toxicology

2.3.1 Mammalian Oral Toxicity

2.3.1.1 Mammalian Oral Toxicity – Acute

There are few data on the acute toxicity of TDG in laboratory animals, although oral LD_{50} values of 3960 mg/kg in guinea pigs (Lewis 1992) and 6610 mg/kg in male rats have been reported (Smyth et al. 1941). A subcutaneous LD_{50} of 4 mg/kg for rats and mice and an intravenous LD_{50} of 3 mg/kg for rabbits were also reported (Anslow 1948); however, these types of exposure are not applicable to oral pathways.

2.3.1.2 Mammalian Oral Toxicity – Subacute

A subacute (14-day) oral toxicity was conducted with TDG in male and female rats to select a suitable dose for a subsequent 90-day study (Angerhofer et al., 1998). Rats were dosed orally with neat TDG at

dose levels 0, (control), 157, 313, 625, 1250, 2500, 5000 and 9999 mg/kg/day for 5 days per week for two weeks. During the 14-day study, food consumption, body weights and any clinical signs were recorded. At the end of 14-day, blood samples were collected for hematology and clinical chemistry and gross necropsies were performed. TDG dosed rats at 5000 or 9999 mg/kg /day showed decreased body weights and increased kidney weights. There were no treatment related changes observed in hematological and clinical parameters. Based on this results LOAEL was 5000 mg/kg/day determined and selected as the highest dose for the 90-day study.

2.3.1.3 Mammalian Toxicity – Subchronic

Subchronic studies relating to the effects of TDG on mammals were available. Angerhofer et al. (1998; 1999 [abstract]) describe an oral gavage study in which "neat" TDG was administered to 10 Sprague Dawley rats/sex/group at 0, 50, 500, or 5,000 mg/kg-day, 5 days/week, for 90 days. Food consumption and body weight changes were monitored weekly, blood and urine samples were collected at term, and samples of organs were excised for histopathological examination at necropsy. Few compound-related clinical signs of toxicity were observed. Those that were observed included a reduction in body weight gain and lower absolute body weight in high-dose animals. There were no changes in the pathology or histology of any organ, although the relative weights of liver, testis and brain were increased in high-dose versus control rats. Finally, potential renal impacts in the high dose group were evidenced by the observed increase in kidney weight, with concomitant increase in the volume of urine and the urine specific gravity, and decrease in urine pH. Granular casts were also observed in the urine. Although urine pH was reduced and specific gravity increased in females from the 500 mg/kg-day dose group, the author's considered this level to represent the no-observed-adverse-effect level (NOAEL). A NOAEL of 357 mg/kg-day was derived by duration, adjusting the 500 mg/kg-day dose to account for the 5 days/week dosing regimen. The associated lowest-observed-adverse-effect level (LOAEL) would be 3,570 mg/kg-day.

2.3.1.3 Mammalian Toxicity – Chronic

No data were available for chronic exposures.

2.3.1.5 Mammalian Toxicity - Other

In addition to the acute and subchronic studies described above, one developmental study and several *in vitro* and *in vivo* studies of TDG were available. Houpt et al. (2001, 2003, 2007) evaluated the developmental toxicity of TDG in Sprague-Dawley rats. Following an initial range-finding study, a gavage study was conducted on positively-mated female rats given doses of 0, 430, 1290 and 3870

mg/kg-day on gestation day 5 through 9. Although the cause of death could not be determined, one female in the high dose group died prior to the end of the study. Additionally, maternal body weights and food consumption were negatively affected during part of gestation (days 16-20 for both parameters, as well as days 5-13 for food consumption) in the high dose group. There was an increased number of fetuses per dam in the high dose group; however, both fetal body weights by litter and by individual fetus were significantly lowered in this dose group compared to controls. TDG was not teratogenic at the dose levels tested, and did not affect other reproductive parameters measured (e.g., number of implantation sites, resorptions, number of live and dead fetuses, and sex ratio). The NOAEL for developmental oral toxicity in rats was 1290 mg/kg-day, when administered during the major period of organogenesis. The corresponding LOAEL based on decreased fetal body growth was 3870 mg/kg-day.

In toxicokinetic studies, sequential reports from Great Britain's Chemical and Biological Defence Establishment at Porton Down, have examined HD metabolism *in vivo* and pointed to the physiological role of TDG as a urinary constituent of human beings and animals exposed to HD. The studies build on work of Wils et al. (1985, 1988) whose demonstration of the presence of TDG in the urine of hospitalized Iranian soldiers lent support to claims of HD use by Iraq in the Iran-Iraq war. While Wils et al. (1985, 1988) derived reconstituted HD by the addition of concentrated hydrochloric acid to urine, the Porton group used a number of technical advances to isolate and detect hydrolysis products (such as TDG and its sulfoxide), and the products of combined glutathione conjugation and β-lyase activity (such as 1,1-sulphonylbis[2-(methylsulphinyl)ethane] and 1-methylsulphinyl-2-[2-(methylthio)ethylsulphonyl]ethane). For example, administration of double-labeled ^{14}C- and ^{35}S-HD to male Porton rats via the intraperitoneal route resulted in the appearance of a substantial number of hydrolysis and glutathione conjugation products of HD, with 60 percent of the load appearing in the urine within the first 24 hours of treatment (Black et al. 1992a). Many of the same products were formed when HD was applied to the skin of Porton rats, although a much lower percentage was released to the urine, even for as long as 8 days after application (Black et al. 1992b). To explain this finding, Hambrook et al. (1993) studied the quantitative recovery of cutaneously applied ^{35}S-HD, and showed that while most of the counts passed into the blood stream, a substantial proportion was retained in the skin, some released as a vapor, and only a small portion transported to the urine. Additionally, their *in vivo* and *in vitro* demonstration of covalent binding of ^{35}S-containing moieties to hemoglobin in red blood cells (RBCs) helped to explain the reduced release of HD metabolites to the urine (Hambrook et al. 1993).

The Porton group reported a number of studies in which they applied their technical advances in TDG detection to urine samples from human beings who had been exposed to HD. In all cases, hydrolysis products and the metabolites of glutathione conjugation and ∃-lyase activity appeared in the urine (Black and Read 1995a,b). Of the former, the sulfoxide of TDG was considered to be a more

important metabolite than TDG itself, while the latter, measured as a single 1,1-sulphonylbis-[2-(methylthio)ethane] derivative, were regarded as more discriminating markers of HD exposure than TDG or its derivatives, because of their complete absence from the urine of unexposed controls.

That the sulfoxide of TDG is the primary hydrolysis product of HD is supported by an experiment in which double-labeled TDG itself was administered intraperitoneally to Porton rats (Black et al. 1993). More than 90 percent of the load was released to the urine within 24 hours, and more than 90 percent of those counts appeared in a peak identified as TDG sulfoxide. Less than 1 percent was unchanged TDG.

Inferential evidence that TDG may have toxicological effects also can be drawn from a report by Brimfield et al. (1995) who, in an *in vitro* experiment, demonstrated the compound's ability to inhibit the serine/threonine protein phosphatase activity of mouse liver cytosol. Vodela et al. (1999a) studied the effects of neat TDG on the glutathione antioxidant system in rats. TDG was given orally at doses of 1250, 2500, and 5000 mg/kg-day for 14 days and at doses of 50, 500 and 5000 mg/kg-day for 90 days of rats obtained from subacute and subchronic studies of Angerhofer et al. 1998. Glutathione reductase levels decreased in females but increased in males given 5000 mg/kg-day for 14 days. No change in the glutathione antioxidant system occurred in the 90-day study. The rat glutathione antioxidant system is thus not a highly sensitive indicator for TDG subchronic exposure. In a related study, Vodela et al. (1999b) evaluated the effects of TDG on the hepatic mixed function oxidase (MFO) system and the cytosolic glutathione antioxidant system in male and female rats gavaged with TDG at 50, 500, and 5,000 mg/kg-day for 90 days. The authors reported an increase in pentoxyresorufin O-dealkylation (CYP2B1/B2) activity (5000 mg/kg-day) and a significant decrease in cytochrome b5 (500 and 5000 mg/kg-day), glutathione (500 and 5000 mg/kg-day), glutathione S-transferases (all doses) and glutathione peroxidase in males (5000 mg/kg-day). There were no significant differences in any of the parameters in female rats. These effects on the MFO and glutathione antioxidant systems generally occurred at a high dose level, indicating that these parameters are not highly sensitive to TDG subchronic exposure.

2.3.1.6 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

Although a degradation product of the extremely toxic chemical warfare agent HD, TDG has been shown to have a low toxicological impact on experimental animals when administered via the oral route. Thus, values for the oral LD_{50} range in excess of 3900 mg/kg body weight, and the few compound-related effects reported in the two available studies (Angerhofer et al. 1998; Houpt 2001) were only observed at very high dose levels (i.e., in excess of 3,000 mg/kg-day). As indicated in Table 2 and Figure 1, the responses of oral administration of TDG were confined to reduced body weight gain in adults and fetuses,

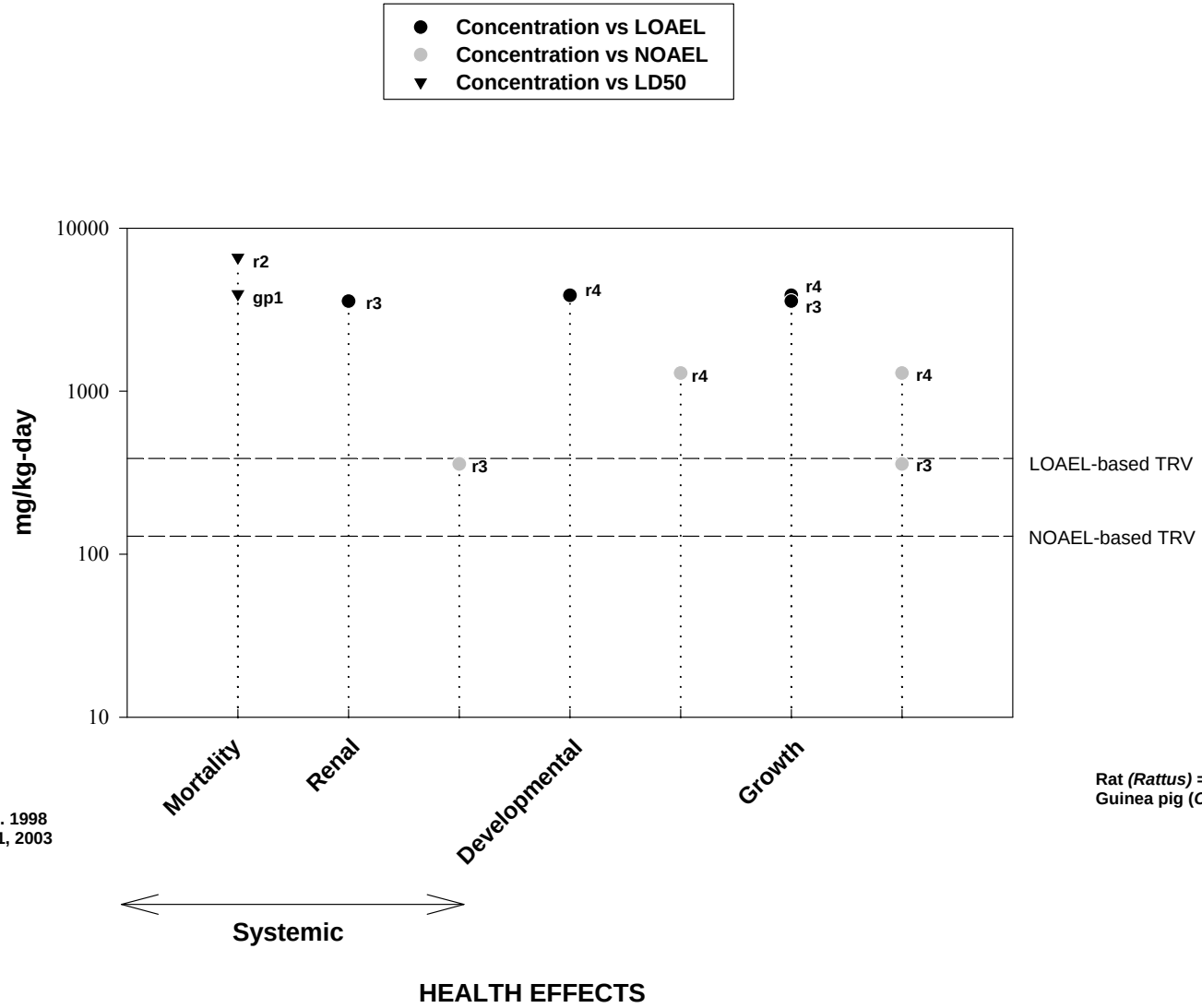
relative increases in some organ weights, and to functional deficits in urine production indicative of possible kidney impairment. These studies are of sufficient quality for TRV derivation.

Table 2. Summary of Relevant Mammalian Data for TRV Derivation

Study	Test Organism	Test Duration	Test Results		
			NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Effects Observed at the LOAEL
Angerhofer et al. 1998 & 1999	Rats (Sprague-Dawley)	90-d	357	3,570	Reduced body weight gain; structural and functional deficits in the kidney
Houpt et al. 2001, & 2003	Rats (Sprague-Dawley)	GD 5-9	1,290	3,870	Decreased maternal body weight and food consumption; decreased fetal body weight

Figure 1

THIODIGLYCOL: HEALTH EFFECTS TO MAMMALS



1 = Lewis 1992
2 = UO 2002
3 = Angerhofer et al. 1998
4 = Houpt et al. 2001, 2003

Rat (*Rattus*) = r
Guinea pig (*Cavia*) = gp

2.3.2 Mammalian Toxicity- Inhalation

Acute inhalation toxicity tests were conducted on neutralized HD solution for the Department of Transportation (DOT) (Muse et al.1977). In these experiments, HD was neutralized by hot water (90°C) hydrolysis to produce a less toxic solution, mostly TDG. Rats were exposed (nose only) to this (in an aerosol) at a concentration of 5.4 mg/L for 4 hours. No overt toxicity or deaths attributed to this hydrolysis product were observed during or after the post exposure period of 14 days. Analysis of the solution showed only a trace amount of HD.

2.3.3 Mammalian Toxicity- Dermal

Two studies reported the toxicological effects of TDG in experimental animals via the dermal route. The first reported a dermal LD_{50} value of 20 mL/kg for rabbits (Union Carbide 1971), and in the second, mild skin irritation in rabbits exposed to 500 mg TDG was observed (Carpenter and Smyth 1946). Union Carbide (1971) also reported moderate eye irritation to 500 mg TDG. Using a density of 1.18 g/mL for TDG (www.chemfinder.com), an LD_{50} of 20 mL/kg is equivalent to 23,600 mg/kg.

Other available studies focused on the dermal absorption of TDG. For example, Hambrook et al. (1993) conducted a quantitative recovery study on the fate of ^{35}S-HD, when applied to the skin of Porton rats. The results of this study demonstrated that, while urine is an important clearance route for the metabolic products of HD, significant portions of the load were retained in the blood through covalent binding of the labeled sulfur atoms to hemoglobin. Counts were detected in the blood for several weeks after an initial 6-hour exposure. The authors confirmed an earlier demonstration that cutaneous application of HD to Porton rats results in urinary formation of both hydrolysis products and glutathione conjugates/ β -lyase metabolites of HD (Black et al. 1992b). Recently Reifenrath et al. (2002) studied dermal absorption of TDG and TDG-contaminated or spiked soils using freshly isolated pig skin in a flow-through cell system. They showed the percent absorption of TDG from Yolo soil (1.9% carbon) as 0.9±0.85% and from Tinker soils (9.5% carbon) as 0.5±0.5% as compared to about 20% absorption from acetone.

2.4 Summary of Avian Toxicology

No studies were identified that examined the toxicological effects of TDG in birds.

2.5 Summary of Amphibian Toxicology

No studies were identified that examined the toxicological effects of TDG in amphibians.

2.6 Summary of Reptilian Toxicology

No studies were identified that examined the toxicological effects of TDG in reptiles.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

Only two studies regarding the oral effects of TDG in mammals were available. From this sparse data, it is difficult to determine the specific target organ for TDG, although Angerhofer et al. (1998) reported adverse effects (e.g., increased kidney weight, increased urine output, and decreased urine pH) that may indicate functional deficits in the kidney. Based on these effects and a reduction in body weight gain, the high dose group in this study (3,570 mg/kg-day) was considered a subchronic LOAEL, and the next lower dose (357 mg/kg-day) was considered a subchronic NOAEL. The LOAEL of 3850 mg/kg-day determined for the available reproductive study (Houpt et al. 2001, Houpt et al 2007) is within the range of the LOAEL reported by Angerhofer et al. (1998). Houpt et al. (2001, 2007) observed a significant decrease in maternal body weight and food consumption, as well as a decrease in fetal body in the high dose group (3,870 mg/kg-day), which they considered the LOAEL. The associated NOAEL for these growth and developmental effects was 1,290 mg/kg-day.

The available toxicological studies include subchronic and gestational exposures; however, long-term studies were not available, and only one species was represented. Because Houpt et al. (2001) evaluated the effects of TDG during a critical life stage (i.e., during gestation), this study is considered chronic in nature (USACHPPM 2000). Additionally, a decrease in fetal body weight may result in reduced survival or fitness of the offspring.

Although Houpt et al. (2001) is a developmental toxicity study with relevant endpoints, the minimum data set requirements as outlined in Section 2.2 (USACHPPM 2000) were not met. Namely, data were not available from at least three studies representing at least three species and two taxonomic orders. Therefore, the approximation approach as described in USACHPPM (2000) was used to develop oral ingestion TRVs for mammals. If an UF of 10 is applied to the NOAEL and LOAEL from Houpt et al. (2007) to account for potential interspecies differences, a NOAEL-based TRV of 129 mg/kg-day and a LOAEL-based TRV of 387 mg/kg-day can be derived.

Given the paucity of available data, it is useful to consider the mortality data in developing an appropriate TRV. If the approximation method is used to extrapolate a TRV from the most sensitive LD_{50} data (guinea pig; using an UF of 100 to estimate a NOAEL and a UF of 20 to estimate a LOAEL), it results in a NOAEL-based TRV of 396 mg/kg-day and a LOAEL-based TRV of 198 mg/kg-day. These are comparable to the NOAEL and LOAEL-based TRV values developed from Houpt et al. (2001), and provide support for the appropriateness of use of the Houpt et al. data. Moreover, TRVs developed from either the mortality or developmental data are protective of adverse effects (i.e. reduced growth and

possible kidney impairment) in rats from subchronic exposures (Angerhofer 1998). Together, these relationships provide a weight of evidence that shows the approximation approach is reasonable when applied to the developmental data. Therefore, the TRVs for the Class Mammalia were derived from the developmental NOAEL and LOAEL for the rat by applying an UF of 10.

Table 3 presents the selected TRVs. A low level of confidence has been given to these TRVs because the available data and representative species are severely limited.

Table 3. TRVs for the Class Mammalia

TRV	Dose	Confidence
NOAEL-based	387 mg/kg/d	Low
LOAEL-based	129 mg/kg/d	Low

3.1.2 TRVs for Ingestion Exposures for Mammalian Foraging Guilds

TRVs specific to particular guild associations (e.g., small herbivorous mammals) have not yet been derived. However, the class-specific TRVs shown in Table 3 may be considered to apply to herbivorous small mammals because rats are members of this guild. As with the class-specific TRVs, only one species is represented and toxicological data are limited, so confidence in the TRVs is low. Data to derive TRVs for other guild associations (e.g., carnivorous mammals) is not available at this time.

3.1.3 TRVs for Inhalation Exposures for the Class Mammalia

Available mammalian inhalation data are limited to one acute study, in which no overt signs of toxicity or death were observed after 4 hours exposure to 5.4 mg/L TDG (Muse et al. 1977). Although inhalation TRVs can not be derived from these data, acute exposures of 5.4 mg/L TDG or less, likely do not result in overt adverse effects.

3.1.4 TRVs for Dermal Exposures for the Class Mammalia

Of the two studies evaluating the dermal toxicity of TDG to mammals, only the LD_{50} data (23,600 mg/kg, Union Carbide 1971) are likely to be applicable to TRV development. Using the approximation method (USACHPPM 2000), a NOEC-based TRV of 236 mg/kg and a LOEC-based TRV of 1,180 mg/kg can be estimated by applying UFs of 100 and 20, respectively. These TRVs are presented in Table 4; however, confidence in these is very low due to the reliance of one LD_{50} value for just one species.

Table 4. Dermal TRVs for the Class Mammalia

TRV	Dose	Confidence
NOEC-based	236 mg/kg	Very Low
LOEC-based	1,180 mg/kg	Very Low

3.2 Toxicity Reference Values for Birds

At this time TRVs for birds can not be derived due to the lack of data.

3.3 Toxicity Reference Values for Amphibians

At this time TRVs for amphibians can not be derived due to the lack of data.

3.4 Toxicity Reference Values for Reptiles

At this time TRVs for reptiles can not be derived due to the lack of data.

4. IMPORTANT RESEARCH NEEDS

Mammalian TRVs derived for TDG have low confidence because only one species is represented and toxicological data are limited. Therefore, additional species and taxonomic orders should be evaluated to provide a greater breadth of interspecific data. In addition, toxicity studies that examine demographic factors such as birth, death, and recruitment would have much greater ecological significance. The additional data would increase confidence in the mammalian TRVs and enable development of TRVs for specific foraging guilds. Inhalation and dermal studies on mammals were limited for TDG, and additional studies for these exposure routes are recommended. TRV derivation for birds, amphibians, and reptiles could not be performed due to the absence of toxicity data for birds, amphibians and reptiles. Before reliable avian, amphibian, and reptilian TRVs can be derived, TDG toxicity in these wildlife classes need to be adequately characterized. Appropriate acute, subacute, subchronic and especially chronic TDG toxicity data derived through biologically relevant exposure routes are needed. Research studies should include experimental models of species genetically, biologically and behaviorally similar to wildlife exhibiting the greatest propensity for toxicant exposure. Experimental design should attempt to mimic both exposure type and duration, and include assessments of long-term effects.

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APPENDIX A

LITERATURE REVIEW

The following files were searched in DIALOG:

File 155 MEDLINE; File 5 Biosis Reviews, File 73 EMBASE, File 76 Life Sciences Collection, and File 185 Zoological Record.

The search strategy for **all Receptors**:

- The expression thiodiglycol and its CAS number.

The strategy outlined above yielded 291 hits that initially were retrieved as *keywords in context* to minimize costs (Tier 1). Articles selected in Tier 1 were then reevaluated as abstracts (Tier 2) prior to retrieval. As noted in Section 2.1, 15 articles on TDG were selected for retrieval (in Tier 2) as being relevant to this survey of the impacts of TDG in wildlife.