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Wildlife Toxicity Assessment for Triacetin

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Acknowledgements

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1. Introduction

Triacetin is a triester of glycerin and acetic acid. It has been used for over seventy-five years for a wide range of uses, including: cosmetic biocide (most often as a fungicide), plasticizer, solvent in cosmetic formulas, food additive (as a flavoring agent and adjuvant), and as a binder for combustible material in solid-rocket propellants. It is also known as glyceryl triacetate, glycerol triacetate, glycerin triacetate, glycerine triacetate, triacetyl glycerine, acetin-tri, 1,2,3-triacetoxypropane, 1,2,3-propanetriol triacetate, 1,2,3-propanetriyl triacetate, and acetic-1,2,3-prepanetriyl ester (Fiume 2003). Common trade names include: Enzactin, Fungacetin, Glyped, Kesscoflex TRA, and Vanay. It is a colorless, oily liquid, that although is most often synthesized, can also be found naturally in cod-liver oil, butter, and other fats (Grant 1972). Reflecting its chemical nature and its widespread use as a Food and Drug Administration generally recognized as safe (FDA GRAS) food additive, there is no U.S. Environmental Protection Agency Integrated Risk Information System (US EPA IRIS) record on triacetin, and no threshold limit values have been established to protect occupationally exposed workers to the compound. The only limitation on triacetin is Good Manufacturing Practice (GMP) requirements set by the FDA (FDA 2005).

Triacetin's potential environmental effects are of particular interest because it is a high production volume chemical. Japan, the leading producer of triacetin, is estimated to produce 5,000 t/yr, compared to the global production of about 10,000-50,000 t/yr (OECD 2002). One Japanese production site that produced 2,000 t/yr was estimated to release about 1,440 kg/yr through wastewater (OECD 2002). In the Unites States, Shackelford and Keith (1976) detected triacetin in samples collected from the Tennessee River, but no concentration levels were reported.

This Wildlife Toxicity Assessment summarizes current knowledge on potentially harmful impacts to wildlife from triacetin exposure. Where possible, emphasis is placed on threshold doses for the onset of toxicological effects, as described in reports of experimental studies. Surveying the threshold dosimetry of the compound may help to establish toxicity reference values (TRVs). These levels could serve as protective exposure standards for all wildlife that may become exposed to triacetin while ranging near 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 electronically searched June 3, 2002, using DIALOG to identify primary reports of studies and reviews on the toxicology of triacetin. A single search was conducted for the compound with no descriptors. A two-tiered approach was used in which all citations were first evaluated as titles and "key words in context." All available abstracts of those articles selected in Tier 1 as possibly relevant to TRV development were then evaluated for relevancy in

Tier 2. For triacetin, 10 articles were marked for retrieval from 119 hits. Details of the search strategy and results are documented in Appendix A.

Additional literature searches were made in March 2004, July 2005, and February 2006; **relevant articles or reports were retrieved, evaluated, and incorporated herein when appropriate.**

2.2 Environmental Fate and Transport

As summarized in Table 1, physical-chemical information applicable to the environmental fate and transport of triacetin comes mostly from (1) the Hazardous Substances Data Bank (HSDB 2002), (2) an on-line information sheet posted by the International Program on Chemical Safety (IPCS 2002), and (3) the National Institute for Occupational Safety and Health's Registry of Toxic Effects of Chemical Substances (RTECS 2002). The body of available evidence suggests that triacetin is unlikely to persist in environmental media. When triacetin is released into the environment, it is believed to degrade rapidly. Due to its low vapor pressure of 0.0033 hPa at 25^{o}C, triacetin most likely exists entirely in the vapor phase in the ambient atmosphere (OECD 2002) where it is degraded photochemically to hydroxyl radicals. An estimated Koc of 10.5 suggests that the compound should readily leach from soil to surface water or groundwater. When in water, degradation is expected to occur rapidly and near completely by hydrolysis, producing glycerol and acetic acid, which are further broken down to carbon dioxide. Because of its high solubility and low vapor pressure in a water medium, 99% of the initial parent compound is believed to remain until hydrolysis is complete (OECD 2002). A linear relationship between degradation rates and increasing alkalinity has been demonstrated for triacetin hydrolysis (HSDB 2002). Although biodegradation is generally accepted to be rapid enough to not cause significant environmental effects, the previous detection of triacetin in the Tennessee River suggests that there may be limited capacity for persistence in surface water (HSDB 2002).

Deposition of triacetin in surface water could result in direct exposure of wildlife via dermal contact and ingestion. Evidence suggests, however, that triacetin is rapidly hydrolyzed by a number of enzymes in most tissues, including: lipase in pig (Serrero et al. 1975) and rat (Barry et al. 1966) small intestines, carboxyesterases in the rat liver and plasma (Murphy and Cheever 1968), electric organ cholinesterase (Mounter and Chetham, 1963), intact cells from the electric eel's organ of Sachs (Rosenberg and Dettbarn 1963), and non-specific tissue esterases (WHO 1975). It is readily metabolized in the gastro-intestinal tract where it is treated similar to a small triglyceride. Triacetin is broken down more efficiently than butterfat, hydrogenated cotton-seed oil, and coconut oil (Deuel and Hallman 1940). As such, triacetin has been shown to have more of a nutritive, than a toxic, effect, as evidenced by being able to be a source of liver glycogen (Deuel et al. 1937). It has also been demonstrated to be utilized as efficiently as glucose when fed in amounts equal in caloric value to 15% glucose (WHO 1975).

Table 1. Summary of Physical-Chemical Properties of Triacetin

CAS No.	**102-76-1**
Molecular weight	218.20
Color	Colorless
Physical state	Oily liquid
Melting point	-78 ^{o}C
Boiling point	259 ^{o}C
Density	1.1562 g/cm^3 at 25 °C
Odor	Faint, fatty odor with bitter taste
Solubility in water	58 g/L at 20-25 °C. 70 g/L at 25 °C. Soluble in acetone, benzene, ethanol, ether, chloroform
Partition coefficients:	0.21 (25^{o}C)
Log K_{ow}	2.5×10^{-1}
Log K_{oc}	1.02
Vapor pressure at 25 ^{o}C	2.48×10^{-3} mm Hg; 3.306 x10^{-3} hPa at 25^{o}C
Henry's Law constant at 25 ^{o}C	No data
Conversion factors	1 ppm = 8.92 mg/m^3
	1 mg/m^3 = 0.11 ppm

Sources: HSDB (2002), IPCS (2002), CRC handbook of chemistry and physics (1993), OECD (2002)

2.3 Mammalian Toxicology

2.3.1 Mammalian Oral Toxicity

2.3.1.1 Mammalian Oral Toxicity—Acute

Most of the data concerning acute oral exposure of triacetin in mammals are reported from non-published sources, with very little, if any, information available regarding methodology. At present, the only reported effect from these studies is mortality expressed as LD_{50} values. A single LD_{50} value from a peer-reviewed journal has been calculated as 9,300 mg/kg rat bw by OECD (2002) from a given literature value of 8.0 ml/kg bw and density of 1.16 g/cm^2 (Lawrence et al. 1974). The remaining LD_{50} values that come from unpublished reports are continually reported as secondary references in review papers. Of these secondary referenced reports, the single acute exposure test with reported methods states an LD_{50} of 6,400 to 12,800 mg/kg bw for rats and 3,200 to 6,400 mg/kg bw for mice (Fassett 1948 & 1955, as reported in Eastman 2004). The lowest LD_{50} value from a secondary source with no described methods is >2,000 mg/kg bw for rats (Unichema Chemie, B.V. 1988, as reported in OECD 2002). This dose limit caused no mortality and, although the signs measured were not reported, no signs of systemic toxicity were observed during the 14-d observation period.

2.3.1.2 Mammalian Oral Toxicity—Subacute

No subacute triacetin mammalian oral toxicity data were identified.

2.3.1.3 Mammalian Oral Toxicity—Subchronic

A rigorous study conducted by the Japanese Ministry of Health and Welfare (MHW 1998) administered triacetin by daily oral gavage at 40, 200, or 1,000 mg/kg bw to male Sprague-Dawley rats for 44-d and females for 41- to 48-d (as reported in OECD 2002). In agreement with most other triacetin toxicity studies, no effects on body weight, food consumption, necropsy findings, histopathological observations, or blood chemistries were observed. What makes this study unique, however, is that this is the only study known to assess reproductive effects of triacetin. Males and females were dosed from two weeks prior to mating, with females dosed to day 3 postpartum. No adverse effects were observed in the mating or fertility indices, gestation length, number of corpea lutea and implantations, implantation, gestation or delivery indices, parturition, maternal behavior at delivery and lactation, number of offspring or live offspring, sex ratio, offspring body weight, and live birth and viability indices. In addition, no adverse toxic effects were found in the offspring. As a result, the NOAEL is considered to be 1,000 mg/kg bw/d for this study.

2.3.1.4 Mammalian Oral Toxicity – Chronic

The only chronic triacetin mammalian oral toxicity study identified was a study attempting to find methods to produce a synthesized diet composed of glycerol, formose sugars, and triacetin for use on long-duration space missions (Shapira et al. 1969). Growing rats (age not specified) were fed diets containing between 20% and 60% triacetin by weight for 90-d. A large loss in weight and considerable mortality was observed at 60%, while no adverse effects were observed at 20%, approximating a daily dose of 10,000 mg/kg bw. No other details relating to the toxicity of triacetin were reported.

2.3.1.5 Mammalian Oral Toxicity – Other

Many LD50 values are reported in Fiume (2003) and OECD (2002), however the details of the unpublished reports' methods are often either unclear or completely missing. Since these studies are often reported in triacetin toxicity summary reports, they warrant some mention here. Gast (1963) reports an LD50 for male Swiss mice to be 1,800 mg/kg bw, and 1,100 mg/kg bw for females (reported in OECD 2002). Mice were also reported to have a range of LD50 values from 3,200 to 6,100 mg/kg bw (Bisesi 1994) and 3,200 to 6,400 mg/kg bw (Anstadt 1976, reported in Fiume 2003). LD50 values for rats are reported as 3,480 mg/kg bw (Li et al. 1941, reported in von Oettingen) and from 6,400 to 12,800 mg/kg bw (Anstadt 1976, reported in Fiume 2003). The only report to have determined an LD50 for rabbits reports this value at >2,000 mg/kg bw (Unichema 1994, reported in OECD 2002).

Two subchronic oral toxicity studies were found, however limitations in study design prevent them from being appropriate for TRV derivation. Lynch et al. (1994) fed Sprague-Dawley rats a diet in which 28.5% of the total calories were supplied by triacetin for 30 days. The rats had ad libitum access to food, but because consumed food amounts were not reported, the actual dose could not be determined. No overt signs of toxicity were reported in these rats. In another triacetin feeding study, Cox (1993) stated that the small sample size (N = 4) prevented any definitive conclusions when triacetin (55% w/w) was fed ad libitum to weanling rats for 60 days. Triacetin dose was unable to be determined because food

consumption was unreported. Though no overt signs of toxicity were observed, triacetin was reported to promote survival and fair growth when compared to the control diet of coconut oil.

The focus of many of the studies was an attempt to modulate nutritional parameters and responses through the repeated oral administration of triacetin to mammals. Imoto and Namioka (1983a) supplemented the basal diet of pigs with triacetin over a 47-day period; the animals increased body weight gain compared to controls and demonstrated a 56 to 59 percent energetic efficiency. Triacetin administration was associated with a decrease in blood glucose and an increase in lactate and ketone bodies; glycogen levels increased in liver, heart, and femoral muscle (Imoto and Namioka 1983b).

A series of reports addresses the comparative nutritive effects of dietary triacetin versus broadly isocaloric diets containing longer-chain triglycerides (Lynch et al. 1994, Lynch and Bailey 1995). When the longer-chain triglyceride diets were made available to male Sprague-Dawley rats for 30 days, bodily fat and protein levels were increased. Fat cell diameters, however, were smaller in animals receiving triacetin compared to those receiving longer-chain triglycerides (Lynch and Bailey, 1995). Some fluctuations were observed in plasma lipid parameters, and the amounts of DNA in intestinal mucosal cells were elevated in rats receiving triacetin compared to either controls or those receiving longer-chain triglycerides, however no overt toxic effects were observed (Lynch et al. 1994).

2.3.1.6 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

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)	LD_{50} (mg/kg)	Effects Observed at the LOAEL
Lawrence et al. 1974	Rat	Single exposure	NA	NA	9,300	NA
MHW 1998	Rat	41 to 48-d	1,000	NA	NA	NA
Shapira et al. 1969	Rat	90 d	10,000	30,000	NA	weight loss, considerable mortality

2.3.2. Mammalian Inhalation Toxicity

An LC50 for rats following a 4 h inhalation exposure to triacetin was determined to be >1.721 mg/L (Unichema Chemie B.V. 1994, as reported in Fiume 2003). Studies conducted by Fassett and Roudabush (1955) reported no adverse toxic effects observed in rats exposed to vapor concentrations of 2.2 mg/L for 6 h/d, 5 d/wk, for 90 days or 72.8 mg/L for 6 h/d for 5 days (Eastman 2004). Because triacetin photodegrades rapidly when in the vapor phase, exposure through environmental inhalation is unlikely.

2.3.3 Mammalian Dermal Toxicity

An unpublished report by Bailey (1976) is the only report of a dermal LD_{50} in mammals; LD_{50} in rabbits was determined to be > 5,000 mg/kg bw (cited in OECD 2002). All other data concerning dermal irritation due to triacetin is from unpublished letters or reports. Previous toxicity reviews re-categorize triacetin from that of a non-dermal irritant (Opdyke 1978, citing Fassett 1963) to a slight dermal irritant (Fiume 2003 and Eastman 2004), citing minimal edema and erythema in two guinea pigs receiving triacetin patches of either 5 or 20 cc/kg for 24 h (Anstadt 1976).

2.4 Avian Toxicology

The only study to assess triacetin toxicity in birds (Hem et al., 1974-75) reported little irritation in male Hubbard broiler chickens immediately following intramuscular injection with 0.5 mL triacetin, with complete disappearance by day 7 (cited in Opdyke 1978).

2.5 Amphibian Toxicology

An LDL_{50} of 150 mg/kg bw in frogs was reported (NIOSH 1976, cited in OECD 2002), however neither study details nor citation date are provided.

2.6 Reptilain Toxicology

No information was identified on triacetin toxicity 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

There are too few triacetin reports that provide detailed methods and are published in peer-reviewed journals to be able to establish a reliable TRV. Lawrence et al. (1974) determined an LD50 of 9,300 mg/kg bw in rats. Shapira et al. (1969) reported a 90-d NOAEL of 10,000 mg/kg bw in rats, and reported a large loss in weight and considerable mortality when rats received a diet containing 60% triacetin (approximately 30,000 mg/kg bw). The only study to observe reproductive effects reported a NOAEL at the highest treatment level of 1000 mg/kg bw over a period of 41- to 48-d.

Triacetin is a high volume production chemical (triglyceride) that has used for a variety of purposes for over seventy-five years. Although one source estimates an approximate annual release rate of 7% from a production site, most toxicity reports and reviews agree that no significant environmental exposure is likely.

The historic doses (oral) used for median lethal exposures suggest that triacetin is a comparatively safe compound regarding its effects on experimental animals. This has prompted the U.S. FDA to regard triacetin as a 'generally recognized as safe' (GRAS) ingredient with no limitations on its conditions of use other than current Good Manufacturing Practice (GMP; 21 CFR 184.1901). In addition, the Cosmetic Ingredient Review (CIR) expert panel reviewed the safety of triacetin and concluded that the compound is safe asused in cosmetic formulations (Fiume 2003).

Therefore, triacetin is considered to be non-toxic and of no significant threat to wildlife. This determination is granted a medium level of confidence due to a lack of current rigorous studies.

Table 3. Selected Ingestion TRVs for the Class Mammalia

TRV	Dose	Confidence
NOAEL-based	Non-toxic	Medium
LOAEL-based	Non-toxic	Medium

3.1.2 TRVs for Inhalation Exposures for the Class Mammalia

Triacetin has been assessed as non-toxic to mammals. Adverse effects could not be observed as a result of high acute oral exposures, and given the low vapor pressure of the compound, is unlikely to be encountered via the inhalation route at exposures exceeding the oral limit dose.

3.1.3 TRVs for Dermal Exposures for the Class Mammalia

Not available at this time

3.2 Toxicity Reference Values for Birds

Not available at this time.

3.3 Toxicity Reference Values for Amphibians

Not available at this time.

3.4 Toxicity Reference Values for Reptiles

Not available at this time.

4 Important Research Needs

The limited sub-standard data available on the toxicity of triacetin indicate the need for more research on the oral, dermal, and inhalation routes of exposure. Considering the limited data now available, chronic mammalian studies, especially low dose chronic exposure studies, are particularly necessary. There is general agreement, however, that triacetin is a low priority chemical.

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Appendix A

Literature Review

A search for triacetin in DIALOG was conducted May 29, 2002, with the following files examined:

File 155 MEDLINE®, File 76 Life Sciences Collection, File 185 Zoological Record Online, File 5 Biosis Previews, File 73 EMBASE, Files 34 and 434 SciSearch. (MEDLINE® is a registered trademark of the U.S. National Library of Medicine.)

The structure was as follows:

For All Receptors:

- The expression triacetin, its CAS Number, and the synonym, glycerol triacetate
- RD (Reduce Duplicates)

As noted in Section 2.1, 119 hits on triacetin were obtained in the initial searches, 10 of which were selected for retrieval.