

Tetrahydrofurfuryl alcohol (THFA) for use in crop production

Executive Summary¹

The following petition is under consideration with respect to the USDA NOP Final Rule:

Petitioned: Addition of tetrahydrofurfuryl alcohol (THFA) to § 205.601, “Synthetic substances allowed for use in organic crop production.”

[Contractor’s Note: Federal regulations require that National List petitions include specific information needed for a comprehensive evaluation of a substance. In the case of the THFA petition, certain information deemed Confidential Business Information (CBI) has been withheld from the contractor by the National Organic Program (NOP). In response to the contractor’s request for disclosure, NOP staff reviewed the CBI and stated that the restricted information “is not germane to the evaluation of THFA in regard to the seven OFPA criteria.” The contractor has complied with the NOP’s directive to proceed with the THFA TAP review.]

Tetrahydrofurfuryl alcohol (THFA) is being petitioned for use as a “pesticidal inert ingredient” in organic agriculture. THFA is synthesized from agricultural byproducts, and has an extensive history of use as a highly versatile, high purity solvent. Due to its relatively benign nature and the fact that it is not oil-based, THFA is generally regarded as a “green” solvent in industrial applications. As mentioned above, evaluation of THFA is made difficult by a lack of specific information regarding its use in agricultural systems.

All three reviewers felt that the substance should be considered synthetic, however they were not in agreement on the use of THFA in organic agriculture. Two reviewers recommended that THFA be allowed for use, based on its utility and benign nature. One reviewer dissented, feeling that the missing information was too substantial to allow an effective review.

Summary of TAP Reviewer Analyses

Synthetic/ Nonsynthetic	Allowed or Prohibited	Notes/suggested annotations:
Synthetic (3) Nonsynthetic (0)	Allowed (2) Prohibited (1)	Reviewer 1: Prohibited Reviewer 2: Allowed, no annotation. Reviewer 3: Allowed, provided it is commercialized as a purified (95% pure) product.

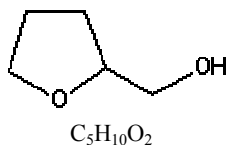
¹This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the contractor’s ability, and has been reviewed by experts on the TAP. The substance is evaluated against the criteria found in section 2119(m) of the OFPA [7 USC 6517(m)]. The information and evaluation presented to the NOSB is based on the technical evaluation against those criteria, and does not incorporate commercial availability, socio-economic impact or others factors that the NOSB and the USDA may consider in making decisions.

Identification

Chemical name:	Tetrahydrofurfuryl alcohol	Other Codes:	
Trade name:	none found	EINECS	603-061-00-7
Other names:	THFA, Tetrahydro-2-furanmethanol, Tetrahydro-2-furylmethanol, Tetrahydro-2-furancarbinol, 2-Hydroxymethyl oxolane	TSCATS	8EH01381-A, 8EH01381-B, 8EH01381-C, 8EH02549-A, 8EH05185-A, 8EH08576-A
CAS Number:	97-99-4	AIRS/AQS	043321
		NIOSH/	LU2450000
		RTECS	
		ICSC	1159
		FEMA	3056
		CCRIS	2923

Characterization

Composition:



Properties (IPCS 1993):

Appearance:	Colorless hygroscopic liquid
Molecular weight:	102.13 g/mol
Solubility (H ₂ O):	moderate
Melting point:	< -80°C
Boiling point:	178°C
Vapor pressure:	30.6 Pa at 20°C
Explosive limits (vol% in air):	1.5-9.7
Stability:	Substance has potential to form explosive peroxides
Reactivity:	Reacts violently with strong oxidants, several N-chloro- and N-bromomides

How Made:

The Petitioner does not manufacture THFA, but rather uses it as an inert ingredient in some of its agricultural products. According to the Petitioner, manufacturing processes for THFA are considered Confidential Business Information (CBI) by the manufacturer and were not available for inclusion in the petition. A literature search revealed that THFA is made commercially from furfural via a high-pressure hydrogenation reaction carried out at 100-1500 psi and at 170-180°C, using a mixture of copper chromate and nickel as the catalyst (Wojcik 1948; Merck 1996). The efficiency of this reaction ranges from 70-80 percent, giving 1,5-pentanediol as a by-product. Furfural, THFA's parent compound, is derived from any agricultural waste biomass rich in hemicellulose (pentosan). Traditionally, furfural has been sourced from corncobs, oat and rice hulls, and sugarcane (IFC, no date).

Specific Uses

THFA is used extensively in various industries as a high-purity, water miscible solvent, and as a chemical intermediate. An informational search yielded numerous applications of THFA-based solvents, including the manufacture of advanced electronics, vinyl resins, dyes for leather, rubber, and nylon. Currently, the largest uses of THFA are in the production of UV curables, THFA acrylates, esters of higher fatty acids (oleic, stearic), and epoxy resin formulations (Schmitt, personal communication). THFA is used as a chemical intermediate in pharmaceutical industry, and is added as an absorption enhancer to various lotions and transdermal medications (Allen 1993). THFA is also being investigated for use as an additive in "clean" fuels, allowing diesel and ethanol to be mixed. In agricultural applications, the substance is used as a cosolvent for active ingredients in pesticide formulations including propiconazole (Alamo, Shepherd), mefenoxam (Platinum Ridomil Gold), and gibberellic acid (Provide).

Status

History of Use:

The introduction of THFA dates back to World War I. During the War, the U.S. began exploring the potential of agricultural wastes in industrial applications. This led to industrial development of furfural (THFA's precursor) in 1922 by the Quaker Oats Company cereal mill in Cedar Rapids (Brownlee and Miner 1948). Quaker Oats pioneered commercial development of various furfural-based compounds through the mid 1950s, using oat hulls, corncobs, and cottonseed hulls as the source biomass. THFA was first synthesized via hydrogenation of furfuryl alcohol in 1955. Recognizing the potential of both these compounds, Quaker Oats opened a sugarcane bagasse-based furfural production plant in Dominica the same year.

Over the past forty years, furfural derivatives have gained worldwide popularity as non-oil-based, highly versatile industrial solvents and precursors to many commercial chemicals. To this day, furfuryl alcohol remains the largest volume derivative of furfural (IFC, 1999). While there are several domestic producers of THFA, the bulk of the compound comes from overseas. In 2002, the U.S. imported 11.4 million pounds of furfuryl alcohol and THFA (US ITA 2002).

Functionality:

The petition requests the use of THFA as a pesticide inert ingredient. The parameters of this use have been withheld from the contractor. Specifically:

Section 3* of the petition requires the Petitioner to state the “intended or current use of the substance...”, and reads as follows:

“Current use: Pesticide *inert* ingredient (solvent used in [CBI – DELETED])”

Section 4 of the petition requires the Petitioner to provide “a list of the crop, livestock, or handling activities for which the substance will be used”, and reads as follows:

“Crop Use: The inert ingredient is used in [CBI – DELETED] that have the following uses [CBI – DELETED]. Not used in handling or processing, thus no mode of action presented.”

Section 8 of the petition requires the Petitioner to provide “...labels of products that contain the petitioned substance” reads as follows:

“Labels: While THFA is not labeled as a pesticide, it is included in [CBI – DELETED] that AMVAC Chemical manufactures and distributed, which are delineated below, and for which labels are appended in III: [CBI – DELETED]”

All other direct references to the substance and its use in agricultural products were deleted from the petition supplied to the contractor.

USDA Final Rule:

The Rule does not mention THFA specifically. In general, inert ingredients are prohibited unless classified by the EPA as List 4 (Inerts of Minimal Concern) and used with a permitted active pesticide ingredient in a passive dispenser (7 CFR 205.601(m)(1)), or when recommended by the NOSB (65 *Fed. Reg.* 80612).

Regulatory

EPA

THFA is regulated under the Toxic Substances Control Act (TSCA) as a chemical in commerce, and appears on the High Production Volume (HPV) 1994 Additions Chemical List. HPV chemicals are those that are manufactured in or imported into the U.S. in amounts equal to or greater than one million pounds per year.

THFA is registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as a List 3 Inert (Inerts of Unknown Toxicity). According to the petition, THFA is in the process of being evaluated for reclassification as a List 4 Inert (Inerts of Minimal Concern), however THFA remains classified as a List 3 Inert at the time of writing this document. Residues of THFA are exempted from the requirement of a tolerance when used as an inert solvent in pesticide formulations and in accordance with GMPs (40 CFR 180.1001(c)).

NIEHS

THFA is not listed in the National Toxicity Program (NTP) database.

FDA

THFA is established as a direct food additive, and appears on the EAFUS (Everything Added to Food in the U.S.) list. THFA is regulated under Title 21 of the Code of Federal Regulations (CFR), and Table 1 summarizes these references.

*The required elements of a National List petition are detailed in the Federal Register [65(135):43260-43261], Submission of Petitions for Evaluation of Substances for Inclusion on or Removal From the National List of Substances Allowed and Prohibited in Organic Production and Handling.

Table 1. FDA References to Tetrahydrofurfuryl alcohol		
21 CFR	Section Heading	Annotation
172.515	Synthetic flavoring substances and adjuvants	Optional adjuvant for use in the minimum quantity required to achieve intended effect, and in accordance with GMPs.
175.105	Components of adhesives	Optional component of adhesive when separated from food by a functional barrier or when using GMPS with certain foods under conditions outlined in § 175.105(a)(2)
176.180	Components of paper and paperboard in contact with dry food	Optional component when used with dry foods listed under § 176.170(c) in the minimum quantity required to achieve intended effect, and in accordance with GMPs.
176.210	Defoaming agent used in manufacture of paper and paperboard	Miscellaneous optional component

U.S. Certifiers

California Certified Organic Farmers (CCOF) Certification Book (2000) – Not listed

Texas Department of Agriculture (TDA) (2000) Organic Certification Program (Materials List) – Not listed.

Quality Assurance International (QAI) (2000) – Defers to OMRI, Not listed.

Midwest Organic Services Association (MOSA) Standards (2001) – Not listed.

Organic Growers of Michigan (OGM) Standards Manual (2000) – Not listed.

Washington State Department of Agriculture (WSDA) Organic Certification Program – Not listed.

Oregon Tilth Generic Materials List (1999) – Not listed.

Organic Materials Review Institute (OMRI) – Approved for use in products appearing on OMRI's Brand Name Products List

International Certifiers

Codex Alimentarius Guidelines CAG/GL 32 (2001) – Not listed.

Int'l Federation of Organic Agriculture Movements (IFOAM) (2002) – Not listed.

Japanese Agricultural Standard (JAS) of Organic Agricultural Products (2001) – Not listed.

European Commission Council Regulation (ECC) No. 2092/91 – Not listed.

Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

- The potential of the substance for detrimental chemical interactions with other materials used in organic farming systems.***

[See **Contractors Note**, above]

- The toxicity and mode of action of the substance and its breakdown products or any contaminants, and their persistence and areas of concentration in the environment.***

Acute Toxicity

LD₅₀ = 0.8-1.6g/kg (guinea pig, oral) (Verschueren 1983)

LD₅₀ = 1.6-3.2 g/kg (rat, oral) (Verschueren 1983)

LD₅₀ = 2,300 mg/kg (mouse, oral) (Lewis 1996)

LD₅₀ = 725 mg/kg (rabbit, iv) (Lewis 1996)

LC₅₀ = >10,000ppm (very low toxicity, frog *Rana bravipoda porosa* tadpoles) (Nishiuchi 1984)

Inhalation: Zero mortality in rats exposed to 655ppm for 6 hr; rats exhibited loss of coordination, prostration and vasodilatation of ears and feet (Clayton and Clayton 1982).

Eye Contact: Rabbits exhibited irritation and increased thickness of cornea at 24 hour after application of 0.1mL (Grant 1986).

Skin Contact: Dermal tests on guinea pigs resulted in minor irritation, and the substance was found not to be a sensitizer. When absorbed through the skin, the LD₅₀ is less than 5mL/kg. (Clayton and Clayton 1982). In comparative tests of penetration enhancers on mice, pure THFA was found to have no ill effect (Lashmar et al 1989)

Mode of Action

[See **Contractor's Note**, above] The mode of action of THFA is not stated by the Petitioner. As an inert solvent used in pesticide products, THFA likely confers favorable physical and/or chemical properties onto the product(s) in which it is used.

Breakdown products/contaminants

The petition states that the substance is used in products at a rate of 6-17 ounces (170-482g) of THFA per acre, or 0.0005 ounces THFA/ft² (152.9 mg/m²) (AMVAC 2002). Based on past measurements, THFA in the soil is expected to be highly mobile (Swann et al 1983; Meylan et al 1992). Should the substance make its way into the hydrosphere, the potential for bioconcentration in aquatic organisms is estimated to be low (Meylan et al 1999).

3. The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*Manufacture*

Manufacturing and processing procedures are considered Confidential Business Information (CBI) and hence are unavailable to the petitioner (who uses THFA as an ingredient in its formulations) or the TAP contractor. The most likely route of industrial synthesis is outlined under the “How Made” section, above.

As mentioned above, THFA is ultimately synthesized from agricultural waste biomass: corncobs, oat hulls, sugarcane bagasse, and other field trash rich in pentosan are converted to furfural, the precursor to THFA. Industrial production and use of THFA in agricultural products may result in its release to the environment (Kottke 1998).

Use, Misuse, and Disposal

[See **Contractor’s Note**, above] THFA is considered an environmentally acceptable solvent in many industrial applications due to its low toxicity, low volatility, biodegradability, and high solvency in organic and aqueous systems (Doyel et al 1992).

THFA is readily biodegraded in sludge (Pitter 1976). The microbe *Ralstonia eutropha* is highly efficient at biodegrading THFA, and tolerates the substance at concentrations up to 200 mM (Zart et al 2001). In terms of abiotic degradation, the substance is not expected to hydrolyze or photolyze (Lyman et al 1990). In vapor form, THFA has an atmospheric half-life of about 13.4 hours (Atkinson 1988), however volatilization is not considered to be a significant fate process (Meylan and Howard 1991; Daubert and Danner 1989).

Disposal

When heated to decomposition, THFA emits acrid smoke and irritating fumes (Lewis 1996).

4. The effects of the substance on human health.

Based on the FDA approval for use as a direct food additive, and its exemption from a tolerance limit by the EPA, THFA does not appear to pose a significant human health when applied at concentrations stated by the Petitioner (0.0005 ounces THFA/ft²).

Potential routes of entry are determined by the nature of use of the substance in agricultural applications. The use(s) remain undisclosed, however a summary of human toxicological effects is presented here for general risk assessment:

By NIOSH estimates, close to 80,000 workers are potentially exposed to THFA in the every year, with the major routes of entry being dermal contact and inhalation of vapor in THFA manufacturing facilities (NIOSH 1983, Parmeggiani 1983). The American Industrial Hygiene Association sets the 8-hr exposure limit at 2 ppm (AIHA 2001). THFA causes severe eye irritation, and it is moderately irritating to the skin and mucous membranes (Lewis 1996).

THFA is non-mutagenic (Maron et al 1981), and is to be considered safe enough for investigation as a solvent for injectable drugs (Mottu et al 2000).

5. The effects of the substance on biological and chemical interactions.

Based on its classification by the EPA as an inert ingredient, detrimental interactions are expected to be minimal. A full assessment of potential interactions requires a more complete understanding of the nature of use.

6. Alternatives to using the substance in terms of practices or other available materials.

The potential of THFA for use as a solvent in agricultural applications has received little attention. Generally, its low toxicity has made it an attractive alternative to other more toxic solvents (Doyel et al 1992). Currently, there are no naturally occurring organic adjuvants on OMRI’s Brand Name Materials List that are registered as solvents per se. A full evaluation of potential alternatives requires specific information about products containing THFA, and their nature of use.

7. The compatibility of the substance with a system of sustainable agriculture

The petitioner readily acknowledges the synthetic nature of THFA (AMVAC, 2002). The Petitioner also goes to great length to support the claims that THFA is environmentally benign and non-hazardous to human health. There is much peer

reviewed evidence to support these assertions. Due to its relatively benign nature and the fact that it is not oil-based, THFA is generally regarded as a “green” solvent in industrial applications. Low toxicity, low volatility, biodegradability, and high solvency in organic and aqueous systems make THFA an attractive substance for use in agricultural formulations. A strong argument can be made that, from the standpoint of environmental sustainability and human safety, THFA is compatible with a system of sustainable agriculture.

A strong counterargument can be made against the approval of a substance based simply on a substance’s benign nature, especially given the lack of information about how THFA is used. Evaluation against OFPA Criteria 1 and 6 in particular require specific information to determine a substance’s potential for agroecosystem interactions. In the absence of this information, a comprehensive review remains elusive, and any judgment derived from it is open to interpretation.

Fundamentally, sustainable agriculture is predicated on a systems approach to production. By definition, a systems approach precludes emphasis of singular components. Similarly, the OFPA criteria were designed as a whole to address the complexity of approving materials for use in organic production. In that sense, viewing OFPA criteria as disparate elements is contrary to the principles of organic agriculture, and makes it difficult to justify the inclusion of THFA in the National List based on incomplete information.

Tap Reviewer Discussion

Reviewer 1 *[PhD in Chemistry; 19 years research experience on organic methods of pest control and IPM; extensive publications on IPM, organic and sustainable agriculture; research experience in toxicology; 5 years experience as a technical advisor on organic materials; Pacific time zone]*

Evaluation of tetrahydrofurfuryl alcohol (THFA) against the Organic Farming Production Act Section 2119 U.S.C. 6518(m)(1-7) Criteria:

1. *The potential of the substance for detrimental chemical interactions with other materials used in organic farming systems.*
It is impossible to make a good prediction of detrimental chemical interactions without knowing the pesticide formulation THFA is used in or how that pesticide will be used.

However, since THFA is an alcohol, it might react with alkaline or acidic products. There might be a problem with lime or Bordeaux mixtures. It might react with acetic acid or citric acid weed killer formulations.

If the formulation is applied through irrigation tubing there could be violent reactions if ozone is used to clean the tubing. According to the petitioner, THFA reacts violently with oxidizing agents.

2. *The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment.*
According to an MSDS cited by the petitioner, the oral LD₅₀ in rats is 1600 mg/kg. According to the ZBET database, the LD₅₀ is 2500 mg/kg. Thus, THFA has fairly low acute toxicity. However, the oral toxicity of ethanol in rats is 13,700 mg/kg. So THFA is much more toxic than ethanol, and has very roughly the same toxicity as methanol (Merck Index 1960). It is more toxic than many other solvents in the ZEBET Database (AMVAC 2002).

The acute toxicity of THFA varies considerably with species and sex. Males are more sensitive than females to the toxic effects. THFA is twice as toxic to guinea pigs as rats. No acute toxicity for dogs is presented by the petitioner. However, canine iv injections of 50 mg/kg have been lethal (Shafer and Adicoff 1970).

Subchronic effects of THFA cited by the petitioner are as follows: “Subchronic exposures (oral, dermal, and inhalation) at relatively high levels, have demonstrated developmental toxicity, reproductive toxicity, and central nervous system depression in either rats, rabbits or dogs... repeated or prolonged exposure to vapors may cause central nervous system depression, and decreased male fertility. Repeated or prolonged dermal contact may cause decreased male fertility. Ingestion may cause developmental effects.” (AMVAC 2002).

According to the petitioner, THFA is not carcinogenic or mutagenic (AMVAC 2002).

Documents cited by the petitioner show the odor threshold in water is 8.6 mg/liter. The No Observed Effect Level (NOEL) for rats is 5 mg/kg. Doses of 10 mg/kg led depression of conditioned reflexes. Doses of 20 mg/kg affected cholinesterase and other enzyme activity (Pozdnyakova 1967).

The mode of action of THFA is most likely as a solvent to improve solubility and dispersion of the active ingredient of a pesticide formulation in water. Rough calculations from data supplied by the petitioner show THFA is at least 75% of the pesticide formulation under consideration.

Since THFA is water soluble, mobile in soil, and not very volatile, it could end up in water (HSDB 2003). According to the petitioner, it degrades quickly when confronted with the microbials of activated sewage sludge (Pitter 1976). Presumably, it degrades quickly in soil. Bioaccumulation in aquatic organisms is not expected (HSDB 2003).

The THFA sold commercially is about 98.5% pure with 0.5% water. Thus, about 1% is impurities. Probable impurities are furfuryl alcohol, or 1,5-pentanediol (AMVAC 2002).

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*

The manufacturing process is not specified by the petitioner. Catalytic hydrogenation of furfural or furfuryl alcohol are industrial preparation methods. According to the TAP reviewer, "Industrial production and use of THFA in agricultural products may result in its release to the environment" (Kottke 1998).

4. *The effects of the substance on human health.*

THFA is an eye irritant and the MSDS warns that it is irritating to skin, may cause nausea, blurred vision, and CNS depression if absorbed, inhaled or orally ingested (AMVAC 2002).

The Merck Index (1960) cautions that chronic inhalation exposure to 100 ppm of tetrahydrofuran, a related chemical, could cause liver damage. The American Industrial Hygiene Association sets the chronic 8 hour inhalation exposure of THFA at 2 ppm (HSDB 2003, AIHA 2001). Presumably, the pesticide formulation will be diluted before it is sprayed, and there will be no exposures of this magnitude. If the pesticide formulation is used in an enclosed space such as a greenhouse, proper ventilation should be provided.

According to the petitioner, sprays of the pesticide formulation will lead to THFA application rates of about 150 mg/m². The NOEL is 5mg/kg (Pozdnyakova 1967), and a 50 kg human would need to ingest 250 mg to reach the NOEL. This exposure might be possible if the formulation were applied at greater than label rates in a closed system. If sprayed outside, exposures should be below the NOEL.

According to the petitioner, the FDA permits addition of THFA to food, and the EPA has set no tolerances for it. The regulatory agencies must not believe there is a human health problem (AMVAC 2002).

5. *The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock.*

According to the petitioner, THFA is rapidly degraded by activated sludge (Pitter 1976). It probably does not bioaccumulate (HSDB 2003, Meylan et al. 1999). Applications of 150 mg/m² should not kill soil microorganisms (Maron et al. 1981). The petitioner states that THFA is not phytotoxic, so it should not kill the crop plants (AMVAC 2002). However, it is impossible to make a complete evaluation of interactions without knowing the pesticide formulation.

6. *The alternatives to using the substance in terms of practices or other available materials.*

The best alternative would be to use another solvent. Ethanol is a non-synthetic List 4 inert that is acceptable in organic agriculture. The acute toxicity of ethanol is about 8x less than that of THFA (Merck Index 1960, AMVAC 2002).

Without knowing the pesticide formulation, pests, or crops it is difficult to make other assessments of alternatives.

7. *Its compatibility with a system of organic agriculture.*

In its favor, THFA is derived from farm products that might otherwise be wasted. Solvents obtained from renewable sources are more compatible with organic agriculture systems than those obtained from petroleum.

However, THFA is a synthetic. It probably is going to be sprayed on food such as apples and tomatoes. If the pesticide formulation is applied near harvest, residues of this synthetic will be ingested by consumers. Organic consumers are expecting to obtain relief from the modern onslaught of ingested synthetic chemicals. Two recent studies show that an average person in the U.S. might be carrying 91 synthetic chemicals, including 17 pesticides or pesticide metabolites (CDC 2002; EWG 2002). THFA in this sense may violate the spirit of organic agriculture.

Do you have any additional references?

The TAP reviewer seems to have found most of the references. However, the petition and/or some of the supporting documents have some very irritating mistakes or misleading statements. On page 10 of the petition, "The possibility of THFA as a candidate to treat induced digitalis toxicity was evaluated in dogs with iv administration of 50 mg/kg THFA.¹⁰ While it was not effective as a treatment, its use as a pharmaceutical candidate is demonstrated in such routine testing." The abstract of the reference (Shafer and Adicoff 1970), which was provided by the petitioner, clearly states that all dogs injected with THFA died. The only ones that lived were those injected only with digoxin.

There is a misleading chart in an article touting low toxicity of THFA versus other solvents. (Doyel et al. 1992) has a bar graph showing the oral LD₅₀ of THFA in rats as about 5500 mg/kg. The LD₅₀ reported by the petitioner is 1600 mg/kg. The ZEBET

Database reports about 2500 mg/kg (AMVAC 2002). The Doyel chart misleads by overestimating toxicity of other solvents and underestimating toxicity of THFA.

Oral toxicity of ethanol shown on Doyel's chart is about 6000 mg/kg, when a standard reference cites 13,700 mg/kg (Merck 1960). The partial ZEBET database supplied by the petitioner has THFA (2500 mg/kg) more toxic than isopropyl alcohol (5800 mg/kg), dimethylformamide (2800 mg/kg), and dioxane (4200 mg/kg). Its toxicity is close to that of cyclohexanol (2060 mg/kg), isobutanol (2460 mg/kg) and methanol (2000 mg/kg). The toxicity information in Doyel et al. (1992) does not check with data from the petitioner or standard references.

CDC (Centers for Disease Control). 2002. CDC's *Second National Report on Human Exposure to Environmental Chemicals*: <http://www.cdc.gov/exposurereport/>

EWG (Environmental Working Group). 2002. *Body Burden: The Pollution in People*: <http://www.ewg.org>

HSDB (Hazardous Substance Databank, National Library of Medicine). 2003. Tetrahydrofurfuryl alcohol. <http://toxnet.nlm.nih.gov/>

Merck Index. 1960. *The Merck Index of Chemicals and Drugs*. Merck and Co., Rahway, NJ. 1642 pp.

Pozdnyakova, A.G. 1967. The determination of the maximum possible content of tetrahydrofurfuryl alcohol in water bodies.

Hygiene and Sanitation 32(2):99-101.[Abstract provided by petitioner]

Shafer, R.B. and A. Adicoff. 1970. Digitalis antagonism by a specific lactone. *Curr. Therap. Research* 12:755-758.[Abstract provided by petitioner]

Recommendations to the NOSB:

(a) Is the material synthetic or non-synthetic?

Tetrahydrofurfuryl alcohol is a **synthetic**.

(b) Should it be allowed, allowed with restrictions (explain) or prohibited as an inert ingredient in unspecified products for use in organic crop production?

Based on the information given, I cannot recommend addition of THFA to the National List of allowed synthetics for organic crop production. Since the pesticide formulation is not specified, no one can get a clear picture of possible interactions and alternatives, and cannot properly evaluate criteria 1 and 6. Without knowledge of the manufacturing method, criterion 3 cannot be answered properly. The petitioner has also not explained exactly why this particular List 3 solvent is necessary. THFA has low toxicity, but many other solvents are less toxic, and several are on List 4.

If the pesticide formulation involved is critically important to organic agriculture, formulation with a List 4 solvent such as ethanol is possible. If the solvent characteristics of THFA are so unique that the formulation is useless without it, the petitioner should ask the EPA to evaluate the toxicity profile of THFA to see if it qualifies for List 4.

* * *

Reviewer 2

[PhD, organic chemistry; 20 years experience in isolation, identification, synthesis, and development of applications for insect pheromones and related compounds; 14 years university extension specializing in transfer of pheromone technology to users; Pacific time zone]

Evaluation of tetrahydrofurfuryl alcohol (THFA) against the Organic Farming Production Act Section 2119 U.S.C. 6518(m)(1-7) Criteria:

1. *The potential of the substance for detrimental chemical interactions with other materials used in organic farming systems.*
There is insignificant potential for detrimental interactions of THFA for interactions with other materials used in organic farming. The only potentially reactive functional group in THFA is the primary alcohol function, which would only react with highly reactive substances such as anhydrides, acid chlorides, and the like, which would never be present in agricultural chemicals because they react violently with water. The alcohol could potentially be oxidized by powerful oxidizing agents, but again, these would never be present in agricultural chemicals because they would destroy the other chemicals present also.
2. *The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment.*
THFA will be used in very small quantities of a few ounces per acre. The toxicity data provided indicates that it presents negligible risk to animals or plants in the amounts and formulations in which it will be used. The compound is relatively volatile, having a boiling point similar to natural compounds such as monoterpenes, as well as being completely miscible with water. Furthermore, the available evidence indicates that it is quite rapidly biodegraded. Although the products of physical and biodegradation are not given, it would likely be broken down into smaller and/or more polar fragments with negligible biopersistence or accumulation in the environment.

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*
The probability of environmental contamination during manufacture cannot be addressed directly because no information on its manufacture was provided. However, the fact that it is made in very large amounts by a number of large, well-established, and reputable companies, both in the US and abroad, that operate under good laboratory and manufacturing standards by law suggests that environmental contamination during manufacture is not an issue. The probability of contamination during use or misuse is negligible because the amount used per acre is so small and the compound has very low toxicity. The probability of contamination during disposal will vary with disposal method. Assuming that the empty containers are rinsed according to the typical protocols for agricultural chemical containers, the risk of environmental contamination from properly rinsed containers would be negligible. Excess or unwanted THFA could also be readily incinerated in any facility licensed to incinerate used solvents and similar materials.

4. *The effects of the substance on human health.*

The acute and subacute toxicity data provided indicate negligible risk to human health. The material is already in use as a food additive, a solvent for intravenous drug injection, and in lotions for dermal application. If there was thought to be a significant risk to human health from this substance, it would not be registered for use in these applications.

5. *The effects of the substance on biological and chemical interactions.*

All data presented suggests that in the amounts proposed for use (a few ounces per acre) there are no significant short term or long term effects of THFA on chemical and biological interactions.

6. *The alternatives to using the substance in terms of practices or other available materials.*

The available data suggests that THFA should have properties as a nontoxic, non-accumulating, environmentally benign adjuvant or solvent that are as good or better than the existing alternatives.

7. *Its compatibility with organic farming practices.*

THFA is found in several natural sources, including lavender and mango oils, and fermented soy products. Given its low toxicity, its low persistence, and its rapid biodegradation, it should be compatible with organic farming practices. It should also be pointed out that it is manufactured from the byproducts of farming, unlike many petroleum-based solvents.

Do you have any additional references?

[The Reviewer did not supply additional references]

Recommendations to the NOSB:

- a) Although THFA has been reported from several natural sources, specifically as a component of plant oils, the commercial substance is derived from processing of agricultural wastes to furfural, followed by high-pressure hydrogenation. In this sense, it is a **synthetic** compound.
- b) The substance should be **allowed** as an inert ingredient/solvent in crop protection/crop production formulations, particularly at the low levels of a few ounces per acre.

* * *

Reviewer 3

[Ph.D. in Physical Organic Chemistry, specializing in the relations between molecular structure and activity in bioactive compounds; 22 years experience in development and testing of agricultural compounds; 10+ years experience on review boards of conventional agriculture research journals; Pacific time zone.]

Evaluation of tetrahydrofurfuryl alcohol (THFA) against the Organic Farming Production Act Section 2119 U.S.C. 6518(m)(1-7) Criteria:

1. *The potential of the substance for detrimental chemical interactions with other materials used in organic farming systems.*
This product (THFA) has low reactivity and modest toxicity. As a primary alcohol, long exposure to air will result in slow oxidation to the more reactive and toxic aldehyde. In the same way, low quality THFA (70-90 percent) may already contain serious quantities of the more reactive aldehyde as well as other unknown compounds. Clearance for any use should certainly require at least 95 percent and preferably 98-99 percent.
2. *The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment.*
As THFA is low in toxicity, there is little concern for the professional use of the product by farm workers skilled in the safe use of liquid chemicals. THFA is flammable and easily ignited on hot summer days. Drums have been known to reach 120-130 degrees under full exposure to the summer sun.

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*
THFA has a low probability of contamination provided handlers are executed following the guidelines for handling any chemical having modest irritation and flammability potentials. The danger of handling THFA depends partly on the air temperature and other weather conditions. The use of maximum protective protocols should always be an option.
4. *The effects of the substance on human health.*
Eye irritation and moderate irritation to the skin and mucus membranes is not a serious problem when the technical people handling THFA are properly trained. It becomes more serious under uncontrolled accidentally exposure. It is important that such exposure be minimized by safe procedures and by proper training and availability of protective clothing.
5. *The effects of the substance on biological and chemical interactions.*
THFA is of low reactivity and toxicity. It is unlikely to cause a serious biological or chemical interaction. However, any exposure should be treated quickly and thoroughly to minimize dermal penetration.
6. *The alternatives to using the substance in terms of practices or other available materials.*
Alternatives to the proposed use of THFA are not known to this reviewer.
7. *Its compatibility with a system of organic agriculture.*
After over a century of use in agriculture and industry, THFA has a proven record of safety throughout many large scale uses. The major negative concerns are modest irritation and flammability in very hot weather. Low toxicity and volatility combine with degradation to harmless metabolites to define THFA as a new ideal organic solvent. While there are no guarantees that potential problems will not arise under unexpected use conditions, the track record for THFA is exceptional.

Do you have any additional references?

[The Reviewer did not supply additional references]

Recommendations to the NOSB:

- a) THFA is essentially a natural product obtained from corn. However, by today's standards, the substance should be considered **synthetic**.
- b) THFA should be **allowed** in organic crop production, **provided it is commercialized as a purified (95% pure) product**.

References

- Allen, LVA Jr. 1993. Compounding Topical Dosage Forms: Ointments, Creams, Pastes and Lotions. Paddock Laboratories, Inc. www.paddocklabs.com/publications/secundum/secart32.html
- American Industrial Hygiene Association. 2001. AIHA 2001 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook. AIHA Press, Fairfax, VA.
- AMVAC. 2002. Petition to National Organic Standards Board (NOSB) for Addition of Synthetic Substance (Tetrahydrofurfuryl alcohol (THFA), CAS No. 97-99-4) to National List for Use in Organic Crop Production. AMVAC Chemical, Newport Beach, California.
- Atkinson, R, Aschmann, SM, Goodman, MA, Winer, AM. 1988. Kinetics of gas-phase reactions of the OH radical with (C₂H₅)₃PO and (CH₃O)₂P(S)Cl at 296 ± 2 K. *Int. J Chem Kinet* 20:273-81.
- Brownlee, HJ, Miner, CS. 1948. Industrial development of furfural. *Indust Eng Chem* 40(2):201-204.
- Clayton, GD, Clayton, FE (eds.). *In: Patty's Industrial Hygiene and Toxicology: Vol. 2A, 2B, 2C: Toxicology.* 3rd ed. John Wiley Sons, New York, NY.
- Doyel, KJ, McKillip, WJ, Shin, CC, Richard, DA. 1992. Comparison of the cyclic ether-alcohol tetrahydrofurfuryl alcohol to other known solvents. *In: Adjuvants for Agrichemicals*, CL Foy (ed.), CRC Press, Boca Raton, FL.
- Grant, WM. 1986. *Toxicology of the Eye*, 3rd ed. Charles Thomas Publisher, Springfield, IL.
- International Furan Chemicals, B.V. 1999. Company website: www.furan.com. Rotterdam, Netherlands.
- International Programme on Chemical Safety (IPCS). 1993. International Chemical Safety Card (ICSC) for Tetrahydrofurfuryl Alcohol.
- Kottke, RH. 1998. *Kirk-Othmer Encycl Chem Techno.* 4th ed., Supp:168. John Wiley & Sons, New York, NY.
- Lasjmar, UT, Hadgraft, J, Thomas, N. 1989. Topical application of penetration enhancers to the skin of nude mice: a histopathological study. *J Pharm Pharmacol* 41:118-121.
- Lewis, RJ. 1996. *Sax's Dangerous Properties of Industrial Materials*, 9th ed., v.1-3. Van Nostrand Reinhold Co., New York, NY.
- Lyman, WJ et al. 1990. *Handbook of Chemical Property Estimation Methods.* pp 7-4, 7-5. Amer Chem Soc, Washington, DC.
- Maron, D, Katzenellenbogen, J, Ames, BN. 1981. Compatibility of organic solvents with the Salmonella/microsome test. *Mutat Res* 88(4):343-50.
- Merck Index. 1996. *Encyclopedia of Chemicals, Drugs, and Biologicals.* S. Sudavari (ed.), Merck and Co., Inc., Whitehouse Station, New Jersey.
- Meylan, WM, Howard, PH. 1991. Bond contribution method for estimating Henry's Law constants. *Environ Toxicol Chem* 10:1283-93.
- Meylan, WM, Howard, PH. 1992. Molecular topology/fragment contribution method for predicting soil sorption coefficients. *Environ Sci Technol* 26:1560-67.
- Meylan, WM, Howard, PH, Boethling, RS, Aronson, D, Printup, H, Gouchie, S. Improved method for estimating bioconcentration/bioaccumulation factor from octanol/water partition coefficient. 1999. *Environ Toxicol Chem* 18(4):664-72.
- Mottu, F, Laurent, A, Rufenacht, DA, Doelker, E. 2000. Organic solvents for pharmaceutical parenterals and embolic liquids: a review of toxicity data. *J Pharm Sci Technol* 54(6):456-69.
- NIOSH 1983. National Occupational Exposure Survey (NOES) 1981-1983.
- Nishiuchi, Y. 1984. Toxicity of agrochemicals to freshwater organism. *Suisan Zoshuku* 32(2):115-119.
- Parmeggiani, L. 1983. *Encycl Occup Health & Safety* 3rd ed., p. 931-2. International Labor Office, Geneva, Switzerland.
- Pitter, P. Determination of biological degradability of organic substances. 1976. *Water Research* 10:231-5.
- Schmitt, Duane. Penn Specialty Chemicals, Inc., Memphis, Tennessee. Personal communication.
- Swann, RL. 1983. *Res Rev* 85:17-28.
- U.S. International Trade Administration. 2002. ITA statistics, <http://www.ita.doc.gov/>
- Verschueren, K. 1983. *Handbook of Environmental Data of Organic Chemicals.* 2nd ed. Van Nostrand Reinhold Co., New York, NY.
- Westpro Chemical Company website. San Diego, California.
- Wojcik, BH. 1948. Catalytic hydrogenation of furan compounds. *Indust Eng Chem* 40(2):210-216.
- Zamt et al. 2001. Catalytic and molecular properties of the quinohemoprotein Tetrahydrofurfuryl alcohol dehydrogenase from *Ralstonia eutrophia* strain bo. *J. Bacteriol.* 183(6):1954-60.