UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

December 21, 2007

MEMORANDUM

SUBJECT: Decision Document for Petition Number 5E6996; vitamin E (CAS Reg. No. 1406-18-4), d-alpha-tocopherol (CAS Reg. No. 59-02-9), dl-alpha-tocopherol (CAS Reg. No. 10191-41-0), d-alpha-tocopheryl acetate (CAS Reg. No. 58-95-7), and dl-alpha-tocopheryl acetate (CAS Reg. No. 7695-91-2)

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OVERVIEW

BASF Corporation is requesting that vitamin E per se and two alcohol and two acetate homologues be exempt from the requirement of tolerance in or on raw agricultural commodities under 40 CFR 180.910 when these substances are used as inert ingredients in pesticide formulations. After looking at the available toxicity and exposure data, EPA recommends that the requested exemption from the requirement of tolerance be granted.

EXECUTIVE SUMMARY

BASF is requesting an exemption from tolerance for vitamin E per se (CAS Reg. No. 1406-18-4) and two alcohol and two acetate homologues. The toxicity data were taken from two international, peer-reviewed evaluations of vitamin E: The Joint FAO/WHO Expert Committee on Food Additives (JEFCA) evaluation of alpha-tocopherol (IPCS 1987) and a recent Food and Agriculture Organization (FAO)/World Health Organization (WHO) expert consultation report (FAO 2001). For exposure, standard models were used along with available data.

In summary, vitamin E has low acute oral toxicity. In subchronic toxicity testing vitamin E appears to elicit systemic toxicity in rats only at high doses, with the target organs being the liver and blood. Vitamin E has not been shown to be neurotoxic, mutagenic, or carcinogenic. Finally, no developmental and reproductive effects have been shown. Based on this information there is no concern, at this time, for increased sensitivity to infants and children to vitamin E when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

Vitamin E will be used as an inert ingredient in pesticide formulations applied to raw agricultural commodities. In addition to exposure through the pesticide application, individuals are exposed to vitamin E through their diet, and can be exposed through topical skin preparations used in cosmetics and skin care. Application of pesticide formulations containing vitamin E is not expected to result in residues of concern. Vitamin E is not persistent in the environment and it does degrade in soil. Vitamin E is an essential nutrient that, by definition, must be obtained through the diet. Foods rich in vitamin E are from plant sources; the vitamin E content of animal foods is generally low. The Agency does not expect to find vitamin E in drinking water. Vitamin E has a high affinity for the soil and is not, therefore, expected to migrate to surface or groundwater. Vitamin E does biodegrade in the environment. Residential dermal exposure is possible through applications of pesticides containing vitamin E, specifically, through the topical application of skin creams containing vitamin E. Vitamin E has been shown to be beneficial as a topical treatment in dermatology.

Taking into consideration all available information on vitamin E, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to vitamin E when used as an inert ingredient in pesticide formulations when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, the exemption from the requirement of a tolerance requested by the petitioner under 40 CFR 180.910, BASF Corporation, for residues of vitamin E, can be considered assessed as safe under section 408(q) of the Federal Food, Drug and Cosmetic Act.

I. BACKGROUND

Vitamin E is the major lipid-soluble antioxidant in the cell antioxidant defense system and is exclusively obtained from the diet. An adequate daily intake of vitamin E is necessary. Deficiencies may cause symptoms such as peripheral neuropathy. However, overt deficiency is very rare, seen only in individuals unable to absorb the vitamin or with inherited abnormalities that prevent the maintenance of normal blood concentrations. Current dietary patterns appear to provide sufficient vitamin E to prevent deficiency symptoms. The National Academy of Sciences (NAS) recommends that the average adult consume 15 mg of vitamin E on a daily basis. (IOM 2000) In addition, NAS recommends that individuals consume no more than 1,000 mg of vitamin E per day—at excessively high doses it can act as an anticoagulant and may increase the risk of bleeding problems. (NIH 2007; IOM 2000) The term "vitamin E" actually refers to a family of eight naturally occurring homologues that are synthesized by plants from homogentisic acid. (FAO 2001). Homologues of vitamin E may exist as alcohols or as esters; chemically esters are called as acetates.

BASF is requesting an exemption from tolerance for vitamin E per se (CAS Reg. No. 1406-18-4) and two alcohol and two acetate homologues (BASF 2005, 2006). Chemically, these substances are very similar and in the body act in the same way. For sake of simplicity, mention of vitamin E in this document (unless otherwise noted) can be considered to be vitamin E per se and/or one of the two alcohols or two acetates. Provided in Table 1 is a list of the substances addressed in this petition along with their CAS numbers, common names, and CAS-9CI names. In general, the EPA Preferred Names are used in Decision Documents. Because these are not available for all the vitamin E homologues under consideration in this petition and the CAS-9CI[1] names are quite cumbersome, the more common names will be used throughout.

Table 1. Nomenclature of Substances Under Consideration in this Petition

Common Name			CAS Reg. No.	CAS-9CI Name
Vitamin E:			1406-18-4	Vitamin E
	Vitamin E Alcohol:	d-alpha-tocopherol	59-02-9	2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, (2R)-
		dl-alpha-tocopherol	10191-41-0	2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-
	Vitamin E Acetate:	d-alpha-tocopheryl acetate	58-95-7	2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R)-4,8,12-trimethyltridecyl]-, acetate, (2R)-
		dl-alpha-tocopheryl acetate	7695-91-2	2H-1-Benzopyran-6-ol, 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-, acetate

[1]Chemical Abstracts Service (CAS) monitors, indexes, and abstracts chemical literature and patents. CAS has developed a systematic nomenclature standard to describe the substances found in literature and patents.

Regulatory

Under an amended Notice of Filing (NOF), (72 FR 16352; April 4, 2007) BASF Corporation is requesting that vitamin E per se and two alcohol and two acetate homologues (see Table 1) be exempt from the requirement of tolerance in or on raw agricultural commodities when these substances are used as inert ingredients in pesticide formulations.

The original NOF was published in January 2006 (71 FR 2925; January 18, 2006) and was limited to a single substance, alpha-tocopherol (CAS Reg. No. 10191-41-0); also, the petitioner requested the exemption under 40 CFR 180.950. BASF asked to amend the petition because it was too narrowly defined:

> "Alpha-tocopherol is known to be the most biologically active form of Vitamin E. However, the ester of alpha-tocopherol (alpha-tocopheryl acetate) is also a common source of Vitamin E. Alpha-tocopheryl acetate is converted to alpha-tocopherol in the body upon ingestion. For purposes of this petition, BASF requests that the acetate and alcohol forms of Vitamin E be viewed as equivalent substances and that the existing petition 5E6996 be amended to include the closely related Vitamin E substances." (BASF 2006)

Between the original and amended NOF one comment was received. The commenter opposed granting this tolerance exemption because she did not want any additives permitted in food; also she raised concern regarding vitamin E and decreased blood clotting. These concerns were addressed in the risk assessment.

Data to Support the Petition

For toxicity, the petitioner relied heavily on two international, peer-reviewed evaluations of vitamin E: The Joint FAO/WHO Expert Committee on Food Additives (JEFCA) evaluation of alpha-tocopherol (IPCS 1987) and a recent Food and Agriculture Organization (FAO)/World Health Organization (WHO) expert consultation report (FAO 2001). For exposure, standard models were used along with available data.

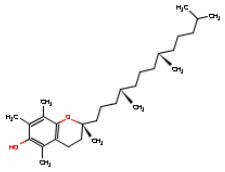
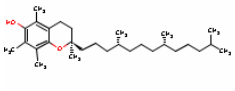
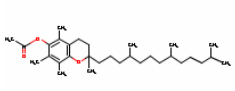
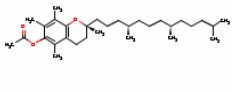
JEFCA. Vitamin E (alpha-tocopherol and mixed tocopherol concentrate) were evaluated for acceptable daily intake at the sixth and seventeenth meetings of JEFCA. Because vitamin E is a nutrient, an acceptable daily intake (ADI) was established. (IPCS 1987)

Expert Consultation Report. A joint FAO/WHO expert consultation report, "Human Vitamin and Mineral Requirements," was published in 2001. It describes the difficulty in determining Recommended Nutrient Intake (RNI) levels for vitamin E, but states that vitamin E appears to have very low toxicity, with 100 to 200 mg/day of the synthetic (dl-alpha-tocopherol) commonly taken as dietary supplements. They note that pro-oxidant damage has been associated with feeding of vitamin E supplements, but typically only at very high levels, e.g., exceeding 1,000 mg/day. (FAO 2001)

II. PHYSICAL AND CHEMICAL PROPERTIES

Provided in Table 2 are some of the physical and chemical characteristics of the vitamin E substances under consideration in this assessment. All structures are from the National Institutes of Health (NIH) ChemID database (NIH 2004). The data for dl-alpha-tocopherol and dl-alpha-tocopheryl acetate was provided by the petitioner (except where noted); the information for d-alpha-tocopherol and d-alpha-tocopheryl acetate is from EPA's EPISuite (EPA 2007a), a model that provides physical/chemical property and environmental fate estimates (and measured data where available) based on a chemical's structure.

Table 2. Physical and Chemical Properties of Vitamin E

	d-alpha-tocopherol (USEPA 2007a)	dl-alpha-tocopherol (BASF 2002b)	d-alpha-tocopheryl acetate (USEPA 2007a)	dl-alpha-tocopheryl acetate (BASF 2002a)
Structure	 (NIH 2004)	 (NIH 2004)	 (NIH 2004)	 (NIH 2004)
CAS #	59-02-9	10191-41-0	58-95-7	7695-91-2
Molecular Weight	430.72	430.7	472.76	472.7
Common Names	alpha-tocopherol; (R,R,R)-alpha-tocopherol; Aquasol E (NIH 2004)	vitamin E; vitamin E alcohol	(+)-alpha-tocopheryl acetate ; (R,R,R)-alpha-tocopheryl acetate (NIH 2004)	vitamin E acetate (NIH 2004)
Physical State		Oily Liquid		Oily Liquid
Melting Point (°C)	202.73 (estimated)		202.99 (estimated)	
Boiling Point (°C)	478.87 (estimated)	Not available	493.41(estimated)	>300°C @ 1 atm
Specific Gravity		Not available		0.95 to 0.96 @ 20°C
Vapor Pressure (mm Hg)	1.35×10^{-8} @ 25°C (estimated)		5.3×10^{-10} @ 25°C (estimated)	3 @ 270°C
Partition Coefficient (log Kow)	12.18 (estimated)		12.26 (estimated)	12.2 (measured)
Water Solubility (mg/L)	3×10^{-7} @ 25°C (estimated)	Insoluble	3.65×10^{-8} @ 25°C (estimated)	Insoluble
Other Solubility				Soluble in many organic solvents
Henry's Law Constant ($atm\text{-}m^3/mole$)	3.6×10^{-6} (estimated)		4.1×10^{-4} (estimated)	

III. HUMAN HEALTH ASSESSMENT

A. Toxicological Data: Petitioner's Submission (BASF 2005, 2006)

For toxicity, the petitioner relied heavily on two international, peer-reviewed evaluations of vitamin E: The JEFCA evaluation of alpha-tocopherol (IPCS 1987) and a recent Food and Agriculture Organization (FAO)/World Health Organization (WHO) expert consultation report (FAO 2001). For exposure, standard models were used along with available data.

Acute Toxicity

The petitioner cited their Material Safety Data Sheet (MSDS) for acute toxicity regarding the dl-alpha acetate and dl-acetate alcohol forms of vitamin E; the results are summarized in Table 3:

Table 3. Summary of Acute Toxicity Data

Parameter	dl-alpha-tocopheryl Acetate (BASF 2002a)	dl-alpha-tocopherol (BASF 2002b)
Oral LD_{50}, rat	>4750 mg/kg	>4750 mg/kg
Eye Irritation, rabbit	Nonirritating	Nonirritating
Skin Irritation, rabbit	Nonirritating	Nonirritating

Subchronic Toxicity

Abdo et al (1986) administered d-alpha-tocopheryl acetate to rats by gavage for 90-days at doses of: 0; 125; 500; or 2,000 mg/kg bw/day. "The lowest [dose] level used was about ten times the level of apparent maximum human consumption." Vitamin E was found to have no effect on body weight or food consumption. However, the liver-to-body weight ratio of females at 2,000 mg/kg bw/day was significantly increased. In males, prolongation of prothrombin and activated partial thromboplastin (APTT) times, reticulocytosis, and a decrease in hematocrit values and hemoglobin concentrations were noted at 2,000 mg/kg bw/day. APTT was also lengthened in females at this dose level. In both females and males hemorrhagic diathesis was seen at 2,000 mg/kg bw/day. "Vitamin E at all doses tested caused interstitial inflammation and adenomatous hyperplasia of the lung." In summary the author concluded that the target organs for the toxicity of vitamin E are the lungs and blood, and possibly the liver.

Chronic Toxicity

Ingestion of large amounts of alpha-tocopherol over long periods of time may cause gastrointestinal distress, muscle weakness, and fatigue. The following are reported in JEFCA (IPCS 1987):

Groups of weanling female Wistar rats were fed diets containing: 0; 25; 250; 2,500; 10,000; or 25,000 IU vitamin E/kg (an "IU" is an international unit, which is a unit of measure used for pharmaceuticals) diet for eight and 16 months. Vitamin E

depressed body-weight gain at concentrations of 10,000 and 25,000 IU/kg diet over the entire length of the study. It increased the relative heart weight at eight months and relative spleen weight at 16 months. There was an increase in plasma alkaline phosphatase and a decrease in the ash content of bone after 16 months at 10,000 and 25,000 IU/kg diet. Prothrombin time was reduced at 12 months, but not at nine or 16 months. Urinary excretion of creatine and creatinine was normal at 11 months. No histological examinations were reported (IPCS 1987 citing, Yang & Desai 1977).

Groups of 60 male and 60 female Charles River CD rats were fed a diet supplemented with dl-alpha-tocopheryl acetate at levels calculated to give a dose of: 500; 1,000; or 2,000 mg/kg bw/day. Occasional difficulties in arresting bleeding were observed when blood samples were collected after eight weeks and frank hemorrhages were observed in males only from week 15 (high-dose), week 16 (intermediate-dose), or week 18 (low-dose). Hemorrhages occurred variously in the gut, urinary tract, orbit and meninges, and from minor injuries to the claws or vibrissal pits. Vitamin K supplementation was effective in bringing about recovery within one to three days. In all other respects, the appearance and behavior of treated animals were similar to controls, and food consumption and body-weight gain were similar to or slightly greater than controls.

Mortality due to hemorrhage in males during the first 26 weeks, maximally 10% in the high-dose group, was balanced by a similar number of deaths in control males between weeks 26 and 52, and thereafter alpha-tocopherol did not adversely affect survival. At termination, there were no significant differences in mortality between any treatment groups of either sex and their respective controls. Prothrombin times were prolonged in males of all treatment groups at week four until week 13, but these returned to normal by week 26 (after initiation of vitamin K supplementation in week 24); females were unaffected. No other hematological differences between treated and control animals were seen except for a transient, slight lowering of the hematocrit and hemoglobin at week eight in both males and females in the highest dose group. Serum alkaline phosphatase was occasionally significantly elevated ($p<0.05$) in the high-dose group, but the differences were not consistent or progressive with time; no such changes were seen at lower-dose levels. A dose-related elevation of alanine aminotransferase was observed in treated males at week four, persisting to week 26, but later it lost statistical significance. Aspartate aminotransferase and all other blood chemical parameters were unaffected, and no significant changes were seen on urinalysis.

At necropsy, no macroscopic changes related to treatment were observed. In females (but not males) of the high-dose group, a slightly elevated absolute liver weight was seen at the interim sacrifice, but the relative liver weight was not increased and no significant differences in relative or absolute organ weights were seen at termination of the study. Histopathological examination of the livers did not reveal any treatment-related changes with the exception of agglomerations of vacuolated (“foamy”) macrophages in the centriacini of some treated rats, distributed among the treated rats without dose-relation, but never occurring in controls. The foamy macrophages stained

strongly with periodic acid schiffs (PAS) and Oil Red O, which distinguished them from occasional peribiliary macrophages seen in controls; they were seen in 17% of treated males and 77% of treated females across the study as a whole. No other treatment-related effects were observed. Whether considered separately by tumor type, or in aggregate, the tumor incidence did not reveal any neoplastic effects of treatment. In both sexes, there were indications of an inverse relationship between dosage and incidence of mammary fibroadenomas, but this effect was statistically-significant only in females (IPCS 1987 citing, Wheldon et al 1983).

Mutagenicity

According to JEFCA (IPCS 1987), alpha-tocopherol is nonmutagenic. The addition of dl-alpha-tocopherol to leukocyte cultures at a concentration of 10 µM reduced by 63% the number of chromosome breaks induced by 1.6 µM 7,12-dimethylbenz(a)anthracene (IPCS 1987 citing, Shamberger et al 1973). dl-Alpha-tocopherol markedly reduced the mutagenic effect of malonaldehyde and ß-propiolactone in five strains of *Salmonella typhimurium*, which mutated with a frameshift mechanism (IPCS 1987 citing, Shamberger et al 1979).

According to the BASF MSDS (BASF 2002a,b) tocopherol and dl-alpha-tocopheryl acetate are nonmutagenic via the Ames Salmonella assay.

Developmental and Reproductive Toxicity

According to JEFCA (IPCS 1987), the results of reproduction/teratology studies did not indicate that alpha-tocopherol had adverse effects on reproductive function at concentrations of up to 2% in the diet.

In a 90-day rat reproduction study conducted using d-alpha-tocopherol (polyethylene glycol) 1000 succinate (TPGS), a water-soluble form of vitamin E, animals were dosed in their diets at concentrations of: 0; 0.002; 0.2; and 2% (or, 0; 2; 200; and 2,000 mg/kg/day). The animals were mated on day 112 of treatment to produce the F1a generation and on day 175 to produce the F1b generation. The F0 animals were maintained on their respective diets to 265 days of treatment, then sacrificed and examined histopathologically. Reproductive indices (mean gestation period, litter size, sex ratio, and mortality of pups or parents) were unaffected by treatment. Clinical chemical and hematological parameters were normal in the F0 generation 10 days before terminal sacrifice (IPCS 1987 citing, Krasavage & Terhaar 1977).

In a mouse teratogenicity study, pregnant animals were given daily doses of 591 mg d-alpha-tocopherol by gavage on days seven to 11 of pregnancy; control animals were untreated or received the same volume of saline by gavage. In a total of 91 offspring from seven litters, one malformation (exencephaly, open eye, and micrognathia) was observed in the offspring from treated animals; no malformations were seen in 177 offspring (13 litters) from untreated dams or 117 offspring (eight litters) from dams given saline by gavage. This type of malformation has never been seen in

control animals of this strain in this testing laboratory, but it can be induced by known teratogens (IPCS 1987 citing, Hook et al 1974).

In a rat teratogenicity study, groups of 15 pregnant Charles River CD rats were given TPGS in the diet at concentrations of: 0; 0.002; 0.2; or 2% (or, 0; 2; 200; and 2,000 mg/kg/day) on gestation days (GDs) six to 16. On day 20, the dams were sacrificed, the uteri excised, and the number of implantation sites (live fetuses, dead fetuses, or resorption sites) were counted. All the fetuses were examined for gross anomalies; half were examined for soft-tissue abnormalities (Wilson technique) and half were examined for skeletal defects (alizarin red stain). No differences were observed between controls and any of the treatment groups with respect to the parameters studied (IPCS 1987 citing, Krasavage & Terhaar 1977).

B. Toxicological Data: Agency Discussion

Provided below is the Agency's discussion of the petitioner's toxicity submission. Where available and appropriate, additional information was considered; they are clearly noted.

Acute Toxicity

The petitioner cited company MSDS for acute toxicity; however, no information was provided regarding the source of the data. The JEFCA report (IPCS 1987) provides acute toxicity data for similar substances; the values are slightly greater than those reported by the petitioner:

> The acute oral LD_{50} values for TPGS and d-alpha-tocopheryl succinate are >7000 mg/kg bw for young adult Charles River CD rats of both sexes (IPCS 1987 citing, Krasavage & Terhaar 1977).

In 2002 the European Union's (EU) Scientific Committee on Food expressed its opinion on the tolerable upper intake level of vitamin E (EU 2003). They pointed out that vitamin E has a very low acute oral toxicity and reported that the LD_{50} for alpha-tocopherol per se is greater than 2,000 mg/kg bw in mice, rats (adult and neonate) and rabbits and for the succinate ester it is >7,000 mg/kg body weight for young adult rats of both sexes (EU 2003, citing Krasavage and Terhaar 1977).

Subchronic Toxicity

Regarding subchronic toxicity, the petitioner referred to a rat study by Abdo et al (1986) where liver and blood effects were seen at 2,000 mg/kg/day in animals dosed with d-alpha-tocopheryl acetate. Also, interstitial inflammation and adenomatous hyperplasia[2] of the lung was seen at all doses tested. Referring back to the literature article for more information on this study, EPA found that the incidence and severity of the lung lesions increased in a dose-dependent fashion. The study investigators did not

[2]"Chronic active or chronic acute interstitial inflammation" (Abdo et al 1986).

address why the lung lesions developed but they did point out that this finding had never been reported in other studies with vitamin E. In summary the author concluded that the target organs for the toxicity of vitamin E are the lungs and blood, and possibly the liver. "A no-effect-level was not observed, since lung lesions were observed in all groups receiving excessive amounts of" vitamin E (Abdo et al 1986). EPA believes that the lung effect is not significant—it was noted in all doses tested and it has not been reported in any other study to date.

In another subchronic toxicity study identified in the literature (IPCS 1987, citing Krasavage & Terhaar, 1977) groups of 30 Charles River CD rats of each sex were fed diets containing TPGS at dietary concentrations of: 0; 0.002; 0.2; or 2% (or 0; 2; 200; or 2,000 mg/kg/day) for 90 days. Hematological and clinical chemical examinations were made on 15 rats of each sex in the control and high-dose groups at 42 and 84 days. At terminal necropsy, organ weights were determined for liver, spleen, brain, pituitary, kidneys, gonads, adrenals, and thyroids, and a histopathological examination was performed. The study investigators concluded that TPGS at the doses studied had no effect on body-weight gain, food consumption, hematology, organ weights, serum chemistry, or histopathology (IPCS 1987, citing Krasavage and Terhaar 1977).

Chronic Toxicity

The petitioner cited two long-term oral studies in the rat, one a 1977 study by Yang & Desai (discussed in IPCS 1987 and EU 2003) and the other a 1983 study by Wheldon et al (discussed in IPCS 1987 and EU 2003). Yang & Desai dosed rats at: 0; 25; 250; 2,500; 10,000; or 25,000 IU vitamin E/kg diet (which is equivalent to[3]: 0; 1.7; 17; 170; 670; and 1,680 mg/kg/day) for eight and 16 months. Depressed body weight gain was seen at 670 and 1,680 mg/kg/day over the entire length of the study. Some organ effects were seen—at the two highest doses increased relative heart weight at eight months and increased relative spleen weight at 16 months. Regarding bleeding, prothrombin time was reduced at 12 months, but not at nine or 16 months. (IPCS 1987 citing, Yang & Desai 1977). The study author concluded that excess vitamin E has deleterious effects. Rats show detectable changes when subjected to excess vitamin E for prolonged periods of time even when all nutrients in the diet are adequate (Yang and Desai 1977).

Wheldon et al dosed male and female rats with dl-alpha-tocopheryl acetate at: 500; 1,000; or 2,000 mg/kg bw/day for 104 weeks. At all dose levels between 15 and 18 weeks the male animals developed spontaneous hemorrhages in the gut, urinary tract, meninges, orbit, and at sites of minor injury. This led to some mortality but in survivors the condition was corrected by administration of vitamin K. (EU 2003) In all other respects, the appearance and behavior of treated animals were similar to controls, and food consumption and body-weight gain were similar to or slightly greater than controls (IPCS 1987).

[3]Using the conversion 1 IU=0.67 mg alpha-tocopherol.

Neurotoxicity

The petitioner did not cite any neurotoxicity findings and none were noted in the published literature.

Mutagenicity

Regarding mutagenicity, the petitioner provided data from the JEFCA report (IPCS 1987) and cited the results of an Ames study (BASF 2002a,b). According to JEFCA, alpha-tocopherol was nonmutagenic. Tocopherol and dl-alpha-tocopheryl acetate are nonmutagenic via the Ames Salmonella assay.

The European Commission (EU 2003) points out that there are no studies designed to investigate the potential genotoxicity of vitamin E per se. However, in studies of the modulating effect of vitamin E on the mutagenicity/clastogenicity (a clastogen is a chemical that will cause a chromosome to break) of other genotoxic compounds, there were no indications of genotoxicity in vitamin E controls.

Carcinogenicity

The petitioner did not provide any information on the carcinogenicity of vitamin E. A search in the National Library of Medicine's TOXNET (HHS no date) yielded no cancer studies per se for any of the vitamin E homologues under consideration in this risk assessment. In discussing the chronic toxicity studies referred to above, the EU (2003) found that "vitamin E displayed no evidence of carcinogenicity in either study."

Developmental and Reproductive Toxicity

To address reproductive toxicity, the petitioner cited a 1977 90-day rat study conducted by Krasavage & Terhaar and summarized by JEFCA (IPCS 1987). Animals dosed with TPGS at doses up to 2,000 mg/kg/day showed no treatment-related effects.

Regarding developmental toxicity, the petitioner referenced a 1974 mouse study by Hook et al (summarized in IPCS 1987) where pregnant animals were dosed by gavage with d-alpha-tocopherol at 591 mg/day on GDs seven to 11. The EU (2003) concluded in their report that "d-alpha-tocopherol was not teratogenic in mice." Another developmental study was conducted by Krasavage & Terhaar in 1977 (summarized in IPCS 1987). Pregnant rats were dosed with TPGS at doses up to 2,000 mg/kg/day on GDs six to 16. No treated-related effects were seen.

The Agency did not identify any further developmental or reproductive toxicity studies.

Summary

In summary, vitamin E has low acute oral toxicity. Alpha-tocopherol has an LD_{50} greater than 2,000 mg/kg bw in mice, rats, and rabbits (EU 2003). In subchronic and chronic toxicity testing vitamin E appears to elicit systemic toxicity in the liver and blood. In subchronic studies, effects in the blood (e.g., increased prothrombin time, decrease in hematocrit which are indicative of bleeding) were seen at high doses (2,000 mg/kg/day). Liver effects were also seen at high doses (2,000 mg/kg/day). In chronic studies, blood and liver effects were seen at high doses (500 and 2,000 mg/kg/day respectively). Vitamin E has not been shown to be neurotoxic, mutagenic, or carcinogenic. Finally, no developmental and reproductive effects have been shown.

Based on this information there is no concern, at this time, for increased sensitivity to infants and children to vitamin E (which includes the chemicals d-alpha-tocopherol; dl-alpha-tocopherol; d-alpha-tocopheryl acetate; and dl-alpha-tocopheryl acetate) when used as an inert ingredient in pesticide formulations. For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

C. Metabolism and Pharmacokinetics

JEFCA (IPCS 1987) reports that the metabolic fate of alpha-tocopherol is not fully known. In a study (IPCS 1987, citing Sternberg & Pascoe-Dawson 1959) where rats were given 3.5 mg daily by month, three to 15% appeared in the feces. With larger doses, up to 25% appeared in the feces. There is practically no urinary excretion of tocopherol but, from studies with labeled material, it appeared that one or more metabolites of tocopherol are excreted in the urine. When more than the daily requirement is administered, there is some storage of tocopherol in the liver (IPCS 1987 citing, Sebrell & Harris 1972).

IV. Environmental Fate Characterization and Drinking Water Considerations

A. Petitioner's Submission (Jackson 2007)

Using publicly-available EPA software, BASF modeled certain environmental fate characteristics and estimated ground and surface water concentrations (Jackson 2007). EPISuite was used for environmental fate; PRZM-EXAMS and SCI-GROW was used for drinking water.

Environmental Fate

Provided in Table 4 is a summary of the environmental fate characteristics provided by BASF (Jackson 2007):

Table 4. Environmental Fate Characteristics of Vitamin E (Jackson 2007)

Fate Characteristic	Value	Source
Log BCF[1]	0.5 (estimated)	EpiSuite
Water Solubility	2.9×10^{-7} to 2.9×10^{-6} mg/L (estimated)	EpiSuite
Henry's Law Constant	3.6×10^{-6} to 7.9×10^{-5} atm m^3/mole (estimated)	EpiSuite
Vapor Pressure	1.4×10^{-8} mm Hg (estimated)	EpiSuite
Log Kow	12.2 (measured)	BASF (2002a)
Log Koc	7.7 (estimated)	EpiSuite
Soil Half-life	180 days (estimated)	EpiSuite

[1]bioconcentration factor

Drinking Water: Surface and Ground Water

BASF (Jackson 2007) used the Agency's PRZM-EXAMS model to provide estimated environmental concentrations (EECs) for surface water. Three cotton and two potato scenarios were modeled. The scenario that yielded the most conservative estimates was that for application to potatoes in Maine. Assuming aerial application with four foliar applications at a rate of 0.036 lb/acre and 14-day intervals yielded a chronic EEC of 0.065 µg/L (ppb). SCI-GROW was used to estimate groundwater concentrations. Accordingly, the model predicted a groundwater concentration of 0.0015 µg/L (ppb).

BASF asserts that it expects no significant exposure to vitamin E via drinking water from its use in pesticides (except in bottled water that contains dietary supplements, where vitamin E may be added intentionally).

B. Agency's Discussion

Vitamin E is a fat-soluble vitamin; it is insoluble in water. Such a substance would be expected be have a high log Kow; BASF has shown this to be the case (their measured log Kow is 12.2). BASF's estimated vapor pressure is the same as EPA's estimated value (see Table 2). Such a vapor pressure—1.4×10^{-8} mm Hg—would be expected for a nonvolatile, oily substance; it will not tend to evaporate. BASF's estimated water solubility and Henry's Law constant are also the same as EPA's estimates.

Regarding drinking water concentrations, EPA expects that little to no vitamin E that is released to the environment during pesticide application will end up in drinking water. Vitamin E has a high affinity for soil, as is evidenced by the estimated log Koc. Any that is released to the environment is expected to adhere to the soil and break down within a year.

In summary, vitamin E is not expected to be persistent in the environment nor is it expected to be found in appreciable amounts in ground or surface water. Modeling data show that it has a high affinity for soil (which means that it will not be transported to drinking water) and that it will degrade within several months of application.

V. Aggregate Exposure Assessment

In terms of pesticides, vitamin E will be used as an inert ingredient in pesticide formulations applied to raw agricultural commodities. In addition to exposure through the pesticide application, individuals are exposed to vitamin E through their diet, and can be exposed through topical skin preparations used in cosmetics and skin care. Provided in the first section below is the Petitioner's Exposure Assessment followed by the Agency's Discussion and Assessment.

A. Petitioner's Assessment (BASF 2005, 2006)

To estimate residues of vitamin E and risk, the EPA Tier I exposure level screening method for inert ingredients was used. By the Tier I method, the maximum estimated chronic exposures range from 0.087 mg/kg/day for adults to 0.422 mg/kg/day for children ages 1 to 2 years. Taking the chronic toxicity endpoint of 50 mg/kg/day for adults, and using a safety margin of 100, gives a calculated chronic population adjusted Dose (cPAD) of 17% for adults. All other population subgroups give cPAD <100 except for children 1 to 2 years, where a chronic toxicity limit of 20 mg/kg/day gives a cPAD of 210%. This subgroup therefore requires a higher level of analysis. The Tier I analysis assumes that the inert is used at the same levels as active ingredients; in reality, the level of Vitamin E use in a pesticide formulation would be far less than half that of the typical active ingredient. Therefore, the estimated exposure can safely be reduced to less than 0.2 mg/kg/day for children 1 to 2 years, giving a cPAD of <100%.

The estimated acute exposures at the 95th percentile of exposure range from 0.199 mg/kg/day for adults to 0.939 mg/kg/day for children 1 to 2 years. A no observed adverse effect level (NOAEL) for acute toxicity is not known, but the LD_{50} for rats is >4750 mg/kg. Scaling this by 100 to estimate for humans, and using a safety margin of 100 gives an acute PAD (aPAD) of 42% for adults. For children 1 to 2 years, this gives an aPAD of 198%. Using similar rationale as with the cPAD analysis, the aPAD calculated with a more realistic formulation use level would be <100% for all population subgroups.

Because the conservative Tier I approach already demonstrates safety, the more detailed and accurate analyses were not made except for estimations where noted. These more refined analyses are expected to point to a much higher margin of safety than estimated here by the Tier I approach.

B. Agency Discussion and Aggregate Assessment

In examining aggregate exposure, the Federal Food, Drug, And Cosmetic Act (FFDCA) section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other nonoccupational exposures, including drinking water (ground water or surface water) and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

EPA does not have information available to assess the potential for exposure to vitamin E in consumer products. Nevertheless, given vitamin E's known role in human physiology and its presence in various foods such as nuts and vegetable oils, it is unlikely that residential exposures of concern would result from the use of vitamin E in nonpesticide products and as an ingredient in pesticide. Therefore, no further aggregate assessment is necessary.

EPA estimated dietary exposures for use of vitamin E as an inert ingredient using a dietary exposure screening model referred to as DEEM™ (USEPA 2007b). DEEM™, or Dietary Exposure Evaluation Model, is a generic screening model that assumes that the inert ingredient is used on all commodities and that 100 percent of crops are treated with the inert ingredient. Further, it assumes finite residues for every consumed commodity (including meat, milk, poultry, and eggs) included in the model. DEEM™ does not include a weight fraction input, but instead is based on a group of active ingredients that are typically found in agricultural food-use products at concentrations ranging from >50% to 100% of the formulation. Provided in Table 5 are the estimated generic chronic exposures for the U.S. population and several subgroups along with the vitamin E exposures (which happen to be the same as the generic exposures[4]). Please note that these estimates are unrefined and very conservative in nature.

Table 5. Estimated Chronic Dietary Exposure for Vitamin E (USEPA 2007b)

Population Subgroup[1]	Generic Estimated Exposure (mg/kg/day)[2]	Vitamin E Estimated Exposure (mg/kg/day)
U.S. Population (total)	0.120	0.120
All infants (<1 year)	0.245	0.245
Children (1-2 years)	0.422	0.422
Children (3-5 years)	0.310	0.310
Children (6-12 years)	0.174	0.174
Youth (13-19 years)	0.100	0.100
Adults (20-49 years)	0.087	0.087
Adults (50+ years)	0.086	0.086
Females (13-49 years)	0.087	0.087

[1]Only representative population subgroups are shown.
[2]Exposure estimates are based on highest tolerance-level residues of high-use active ingredients for all food forms including meat, milk, poultry, and eggs.

In addition to exposure from use in pesticides, individuals are exposed to vitamin E through their diet. Vitamin E is an essential nutrient that, by definition, must be obtained through the diet. Foods rich in vitamin E are from plant sources; the vitamin E content of animal foods is generally low (NRC 1989). "Vegetable oils are the richest source of vitamin E. Other good sources include nuts, seeds, whole grains, and wheat germ." (NRC 1989)

[4]The generic exposures and vitamin E exposures are the same because it was assumed that vitamin E would be used at a concentration of 100%. If a lower concentration of vitamin E were assumed, the generic exposures would be adjusted accordingly.

To ensure health, NAS recommends that adults consume 15 mg of vitamin E per day (or about 0.21 mg/kg/day); this is the Recommended Daily Allowance or RDA (IOM 2000). “A large and growing body of experimental evidence suggests that high intakes of vitamin E may lower the risk of some chronic diseases, especially heart disease.”

Regarding drinking water, based on modeling and what is known about the environmental fate properties of vitamin E, The Agency does not expect contributions of concern from the application of pesticide products containing vitamin E as an inert ingredient. Vitamin E has a high affinity for the soil and is not, therefore, expected to migrate to surface or groundwater. And, it does biodegrade in the environment. The petitioner points out that some bottled drinking waters may now contain vitamin E, with it having been added intentionally as a supplement.

Finally, residential dermal exposure is possible through applications of pesticides containing vitamin E, specifically, through the topical application of skin creams containing vitamin E. “Although topical α-tocopherol is mostly used as concentrations of 5% or less, products with concentrations of 0.0001% and more than 20% vitamin E and/or vitamin E esters have been developed and marketed in Europe and the United States” (Thiele 2005).

VI. Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to vitamin E (CAS Reg. Nos. 1406-18-4; 59-02-9; 10191-41-0; 58-95-7; and 7695-91-2) and any other substances and, this material does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that vitamin E (CAS Reg. Nos. 1406-18-4; 59-02-9; 10191-41-0; 58-95-7; and 7695-91-2) has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs (OPP) concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

VII. Ecological Exposure Assessment

A. Ecological Data

BASF (Jackson 2007) modeled potential ecological toxicity of vitamin E to aquatic organisms such as fish, invertebrates, and algae by using an Agency software application that relies on Structure Activity Relationships or SARs (i.e., ECOSAR[5]); results are provided in Table 6:

Table 6. Estimated Ecological Risk to Vitamin E

ECOSAR Class	Organism	Duration	Endpoint[1]	ng/L
Neutral Organic (Baseline Toxicity)	Fish	14-day	LC_{50}	0.76
Phenols	Fish	96-hr	LC_{50}	33
Phenols	Daphnid	48-hr	LC_{50}	1590
Phenols	Green Algae	96-hr	EC_{50}	0.2
Phenols	Fish	30-day	chronic toxicity	4.06
Phenols	Fish	90-day	chronic toxicity	14.2
Phenols	Daphnid	21-day	chronic toxicity	3.72
Phenols	Green Algae	96-hr	chronic toxicity	7.3

[1]LC is lethal concentration; EC is environmental concentration.

BASF concluded that the ECOSAR calculations indicate that vitamin E is not expected to bioaccumulate. Further, because the compound has such a high adsorption coefficient (estimated log Koc of 7.7) the molecule should bind tightly to soil and other matrices such as plant tissues. Therefore, it is very unlikely the molecule would move off target.

B. Agency Discussion

EPA generally agrees with BASF's analysis and conclusion. They used standard, publicly-available software to model potential ecological risk to aquatic species being exposed to vitamin E.

A search using NIH's PubMed (August 17, 2007) yielded no useful information on the ecological effects of vitamin E in the environment. A review of EPA's ECOTOX database (USEPA 2007c) showed the results of a study looking at the effects of vitamin E on the Zebra mussel. The test organisms in freshwater were dosed once with 50 ppm vitamin E and exposed for 48 hours. The only effect noted was behavioral (ability to detach from substrate).

[5]EPA's ECOSAR model (USEPA 2000), which stands for ECOlogical SAR, predicts the aquatic toxicity of chemicals based on their similarity of structure to chemicals for which the aquatic toxicity has been previously measured. The acute toxicity of a chemical to fish (both fresh and saltwater), water fleas (daphnids), and green algae has been the focus of the development of SARs. SARs are developed for chemical classes based on measured test data that have been submitted by industry or they are developed by other sources for chemicals with similar structures (e.g., phenols).

VIII. Risk Characterization

A. Human Health

BASF Corporation is requesting that vitamin E per se (CAS Reg. No.1406-18-4) and two alcohol (CAS Reg. Nos. 59-02-9 and 10191-41-0) and two acetate (CAS Reg. Nos. 58-95-7 and 7695-91-2) homologues be exempt from the requirement of tolerance in or on raw agricultural commodities under 40 CFR 180.910 when these substances are used as inert ingredients in pesticide formulations. In considering the potential risk posed by the use of vitamin E as an inert ingredient in a pesticide formulation, the Agency considered available toxicity and exposure information.

In summary, vitamin E has very low acute oral toxicity. It has an LD_{50} greater than 2,000 mg/kg bw in mice, rats, and rabbits (EU 2003). In subchronic toxicity testing vitamin E appears to elicit systemic toxicity in rats at high doses, with the target organs being the liver and blood. Effects in the blood were also seen in some of the chronic toxicity studies at high doses, as were slight liver effects. Vitamin E has not been shown to be neurotoxic, mutagenic, or carcinogenic. Finally, no developmental and reproductive effects have been shown. Based on this information there is no concern, at this time, for increased sensitivity to infants and children to vitamin E (which includes the chemicals d-alpha-tocopherol; dl-alpha-tocopherol; d-alpha-tocopheryl acetate; and dl-alpha-tocopheryl acetate). For the same reason, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

To characterize the chronic dietary risk resulting from the use of vitamin E as an inert ingredient, EPA estimated dietary exposure (see Table 5) and compared it to a toxicity endpoint. In the Pesticide Program the 'population adjusted dose' or 'PAD' is commonly used as the toxicity endpoint for dietary risk assessment. A PAD is a reference dose (RfD) that has been adjusted to take into account the Food Quality Protection Act (FQPA) Safety Factor. For vitamin E, EPA is using the "Tolerable Upper Intake Level" (UL) as the toxicity endpoint for risk characterization. Because the NAS Dietary Reference Intakes (DRIs), which include the UL, have been so extensively peer-reviewed, are so widely accepted, and were developed for dietary assessment purposes EPA believes that using these for its dietary risk assessment is appropriate.

The NAS Institute of Medicine (IOM) establishes DRIs which are "reference values that are estimates of nutrient intakes to be used for planning and assessing diets for apparently healthy people" (IOM 2000). DRIs include: RDAs and ULs. An RDA is "the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) of healthy individuals in a particular life stage and gender group." A UL is "the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases." The IOM Food and Nutrition Board (IOM 2000) has established ULs and RDAs for vitamin E; they are provided in Tables 7 and 8, respectively. The critical adverse effect for the vitamin E UL is an increased

tendency to hemorrhage and the level is 1,000 mg/day (for adults) of any form of supplemental alpha-tocopherol (IOM 2000).

Table 7. Tolerable Upper Intake Levels (UL)[1] for alpha-Tocopherol (mg/kg/day)

Age Group (years)	Vitamin E Level (mg/kg/day)		
	Males and Females	During Pregnancy (females only)	During Lactation (females only)
1 to 3	15.0	NA	
4 to 8	13.3		
9 to 13	14.6		
14 to 18	12.8	14.1	14.1
19 >	13.9	15.3	15.3

[1]ULs, as reported by IOM (2000), range from 200 to 1,000 mg/day for the various age groups. EPA assumed that a 1 to 3 year-old weighs 13.3 kg; a 4 to 8 year-old weighs 22.6 kg; a 9 to 13 year-old weighs 41.1 kg; a 14 to 18 year-old weighs 62.6 kg; and an average adult weighs 71.8 kg. In addition, EPA assumes that a 14 to 18 year-old female weighs 56.9 kg and a 19 to 50 year-old female weighs 65.4 kg. (USEPA 1997)

Table 8. Recommended Dietary Allowances[1] for alpha-Tocopherol (mg/kg/day)

Age Group (years)	Vitamin E Level (mg/kg/day)		
	Males and Females (mg/kg/day)	During Pregnancy (females only)	During Lactation (females only)
1 to 3	0.5	NA	
4 to 8	0.3		
9 to13	0.3		
14 to18	0.2	0.3	0.3
19>	0.2	0.2	0.3

[1]RDAs, as reported by IOM (2000), range from 6 to 19 mg/day. EPA assumed that a 1 to 3 year-old weighs 13.3 kg; a 4 to 8 year-old weighs 22.8 kg; a 9 to 13 year-old weighs 41.0 kg; a 14 to 18 year-old weighs 60.6 kg; and an average adult weighs 71.8 kg. In addition, EPA assumes that a 14 to 18 year-old female weighs 56.9 kg and a 19 to 50 year-old female weighs 65.4 kg. (USEPA 1997)

Comparing estimated dietary exposure (see Table 5 for details of calculations) to the appropriate UL's (see Table 7), a metric of dietary risk is calculated; it is expressed as '% of the UL.' Provided in Table 9 is a summary of the estimated '% of the UL.'

Table 9. Estimated Chronic Dietary Risk for Vitamin E (USEPA 2007b)

Population Subgroup[1]	Estimated Exposure to Vitamin E (mg/kg/day)[2]	UL's[3] (mg/kg/day)	Risk Metric ('% of the UL')[4]
U.S. Population (total)	0.120	13.9	0.86
All infants (<1 year)	0.245	15.0	1.6
Children (1-2 years)	0.422	15.0	2.8
Children (3-5 years)	0.310	13.3	2.3
Children (6-12 years)	0.174	14.6	1.2
Youth (13-19 years)	0.100	12.8	0.78
Adults (20-49 years)	0.087	13.9	0.63
Adults (50+ years)	0.086	13.9	0.62
Females (13-49 years)	0.087	13.9	0.63

[1]These are representative population subgroups from DEEM™
[2]See Table 5.
[3]See Table 7
[4]Calculated by dividing the Estimated Exposure by the UL and multiplying by 100.

As shown in Table 9, the '% of the UL' for the overall U.S. population is less than one percent; the percent of the UL for young children is less than three percent. Please note that these estimates of dietary risk, which represent the contribution for food only, are very conservative.

Looking at the other potential sources of vitamin E exposure: on a daily basis average adults should consume 0.2 mg/kg/day (this is the RDA) of vitamin E to maintain health (IOM 2000). Ideally this is achieved naturally, via consumption of foods in our diet that are rich in vitamin E. Contrasting the amount of vitamin E that EPA expects an average adult to be exposed to through use of vitamin E as an inert ingredient (0.0012 mg/kg/day), the pesticidal exposure is quite small. Residues of vitamin E in drinking water are expected to be negligible. While residential exposure is possible from use of pesticides, dermal toxicity is low. Vitamin E is used in certain skin creams. Thiele et al (2005) believes that adverse side effects resulting from topical use of vitamin E are rare. They report that although vitamin E and its derivatives are widely used in many topical cosmetic products (at concentrations up to 36%), "reports of sides effects, such as allergic or irritant skin reactions, are rare."

Taking into consideration all available information on vitamin E (CAS Reg. Nos. 1406-18-4, 59-02-9, 10191-41-0, 58-95-7, and 7695-91-2), it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to vitamin E when used as an inert ingredient in pesticide formulations when considering dietary exposure and all other nonoccupational sources of pesticide exposure for which there is reliable information. Therefore, the exemption from the requirement of a tolerance requested by the petitioner under 40 CFR 180.910, BASF Corporation, for residues of vitamin E, can be considered assessed as safe under section 408(q) of the FFDCA.

B. Ecological

Given what is known about the acute toxicity of vitamin E in animals, the environmental fate characteristics of vitamin E (ability to break down; propensity to adhere to soil and thus unlikely to wash into surface waters), and the results of the modeling which show that vitamin E is not toxic to aquatic organisms such as fish, invertebrates, and algae, EPA does not expect that vitamin E will cause adverse effects to organisms in the natural environment.

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