

US EPA ARCHIVE DOCUMENT



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

February 22, 2005

ACTION MEMORANDUM

SUBJECT: Inert Ingredient Tolerance Reassessment - Adenosine (CAS Reg. No. 58-61-7)

FROM: Dan Rosenblatt, Chief
Minor Use, Inerts, and Emergency Response Branch

TO: Lois A. Rossi, Director
Registration Division

I. FQPA REASSESSMENT ACTION

Action: Reassessment of one (1) inert ingredient exemption from the requirement of a tolerance.

Chemical and Use Summary: See table below.

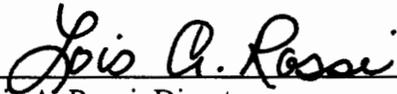
Tolerance Exemption Being Reassessed				
Tolerance Exemption Expression	CAS Reg No.	40 CFR §	Use Pattern (Pesticidal)	List Classification
Adenosine	58-61-7	180.920 ^{1/}	Synergist; Maximum of 0.5% of formulation	4B

1. Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.100(d)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops only.

List Reclassification Determination: Adenosine is classified as a list 4B inert ingredient. Based on the reasonable certainty of no harm safety finding and the existing 40 CFR §180.920 use limitation, the List 4B classification for adenosine is affirmed.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the one (1) exemption from the requirement of a tolerance for the inert ingredient adenosine, and with the List reclassification determination, as described above. I consider the one (1) exemption from the requirement of a tolerance for adenosine established in 40 CFR §180.920 [formerly 40 CFR§180.1001(d)] to be reassessed as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.



Lois A. Rossi, Director
Registration Division

Date:

February 25, 2005

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

February 22, 2005

MEMORANDUM

SUBJECT: Reassessment of the Exemption from the Requirement of a Tolerance for Adenosine

FROM: Kerry Leifer, Inerts Team Leader
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

A handwritten signature in black ink, appearing to read "K. Leifer", written over the typed name in the "FROM:" field.

TO: Dan Rosenblatt, Chief
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

Background

Attached is the science assessment for adenosine. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, and environmental fate and ecotoxicity of adenosine. The purpose of this document is to reassess the existing exemption from the requirement of a tolerance for residues of adenosine as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates adenosine (CAS Reg. No. 58-61-7), a pesticide inert ingredient for which an exemption from the requirement of a tolerance exists for its residues when used in pesticide formulations applied to growing crops only under 40 CFR §180.920 [formerly 40 CFR §180.1001(d)].

Adenosine is a nucleoside that is essential to the functioning of all living organisms. The phosphorylated form of adenosine, adenosine triphosphate (ATP) is the universal carrier of energy in all living cells. The available toxicological/pharmacological data available on adenosine do not identify any toxicological concerns associated with exposure to adenosine and the metabolism of adenosine in humans is well understood. Adenosine is readily degraded in the environment, with any potential exposures resulting from the use of adenosine as an inert ingredient being at levels far less than found endogenously in living organisms.

Taking into consideration all available information on adenosine, including the essential role it plays in all living organisms, its well-understood synthesis and metabolism, lack of toxicity concerns, and the amount of adenosine present endogenously in living organisms, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to adenosine when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemption from the requirement of a tolerance established for residues of adenosine in/on raw agricultural commodities can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report evaluates adenosine (CAS Reg. No. 58-61-7), a pesticide inert ingredient for which an exemption from the requirement of a tolerance exists for its residues when used in pesticide formulations applied to growing crops only under 40 CFR §180.920 [formerly 40 CFR §180.1001(d)].

Adenosine is a naturally occurring substance that is present in all living organisms. Adenosine is a nucleoside consisting of ribose (a five-carbon sugar) bound to the purine base adenine. It is present in a chemically combined form as a component of nucleic acids as well as in smaller amounts in the free form. The phosphate esters of adenosine are adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP), which are three interconvertible nucleotides in which adenosine is attached through its ribose group to one (monophosphate), two (diphosphate), and three (triphosphate) phosphoric acid molecules. Adenosine, AMP, ADP, and ATP all play essential roles in energy storage and energy metabolism; all living cells utilize energy that is stored in the form of the ATP molecule derived from adenosine.

Adenosine and the adenosine-derived nucleotides are crucial to countless biochemical processes including the formation of ribonucleic acid (RNA), protein synthesis, photosynthesis, muscle contraction, and intracellular signal transduction.

II. Use Information

Pesticides

The tolerance exemption for the inert ingredient adenosine is given in Table 1 below.

Table 1. Tolerance Exemption Being Reassessed in this Document				
Tolerance Exemption Expression	CAS Reg No.	40 CFR §	Use Pattern (Pesticidal)	List Classification
Adenosine	58-61-7	180.920 ^{1/}	Synergist; Maximum of 0.5% of formulation	4B

1. Residues listed in 40 CFR §180.920 [formerly 40 CFR§ 180.100(d)] are exempted from the requirement of a tolerance when used as inert ingredients in pesticide formulations when applied to growing crops only.

Other Uses

Adenosine has use in pharmacological applications as an intravenously administered antiarrhythmic agent and ischemic heart disease diagnostic aid adjunct.

III. Physical and Chemical Properties

Table 2 below lists some of the physical and chemical characteristics of adenosine.

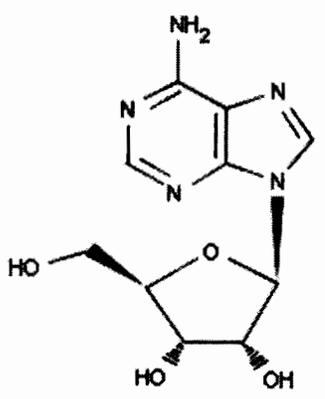
Table 2. Physical and Chemical Properties of Adenosine (CAS Reg. No 58-61-7) Measure (M) or Estimated (E)		
Parameter	Value	Source
Structure		ChemIDplus, 2005
Molecular Weight	267.244	ChemIDplus, 2005

Table 2. Physical and Chemical Properties of Adenosine (CAS Reg. No 58-61-7) Measure (M) or Estimated (E)		
Parameter	Value	Source
Water Solubility	8230 mg/L at 25°C (E)	ChemIDplus, 2005
Melting Point	235.5 ° C (M)	ChemIDplus, 2005
Henry's Law Constant	1.11 x 10 ⁻²² atm-m ³ /mole @25°C (E)	EPISuite, 2004
Vapor Pressure	7.00 x 10 ⁻¹⁵ mmHg @25°C (E)	EPISuite, 2004
Octanol/Water Partition Coefficient	log P = -1.05 (E)	EPISuite, 2004

IV. Hazard Assessment

A. Hazard Profile

Adenosine is a naturally occurring substance that is present in the cells of all living organisms and which is essential for cell function and organism survival; there are no toxicity concerns associated with exposure to adenosine . No adverse effects have been reported associated with the pharmacological use of adenosine.

B. Toxicological Data

There are few references to toxicity studies on adenosine in the scientific literature. A summary of the more pertinent available toxicological data is given in Table 3 below.

Table 3. Summary of Toxicity Data for Adenosine				
Test	Species	Method/ Duration	Result	Source
Oral LD ₅₀	Mouse	single dose	20,000 mg/kg	Amer. J. of Emer. Med., 1996 as cited in ChemIDplus, 2005
Bacterial Reverse Mutation Test	<i>S. Typhimurium</i> , TA 98 and TA 100	<i>in vitro</i> without activation	Negative	McCartney, et al 1985 as cited in CCRIS, 2005

**Table 3.
Summary of Toxicity Data for Adenosine**

Test	Species	Method/ Duration	Result	Source
Bacterial Reverse Mutation Test	<i>S. Typhimurium</i> , TA 97, TA 98, TA 100, TA1535, TA1538	<i>in vitro</i> with and without activation	Negative	Guzzie, 1991 as cited in CCRIS, 2005
Chromosome Aberration Assay	Chinese Hamster Ovary	<i>in vitro</i> with and without activation	Negative	Guzzie, 1991 as cited in CCRIS, 2005

C. Metabolism And Pharmacokinetics

Data from the pharmaceutical use of adenosine demonstrate that adenosine has a very short biological half-life (less than 10 seconds) where, following intravenous administration, it is very rapidly degraded by circulating enzymes to iosine and then further degraded to hypoxanthine, xanthine, and, ultimately, uric acid (Olin, 1990). Thus, the body is readily able to metabolize adenosine.

D. Special Considerations for Infants and Children

Adenosine is a nucleoside that is essential for the functioning of human life, therefore a safety factor analysis has not been used to assess the risks resulting from the use of adenosine, therefore an additional tenfold safety factor for the protection of infants and children is unnecessary.

V. Exposure Assessment

Adenosine is synthesized endogenously and is present in the cells of all living organisms, where it is utilized in a number of metabolic processes including energy transport. The average adult human generates enough metabolic energy to synthesize his or her own weight in ATP every day (Mathews, 1999). Adenosine is also released from the cell, where it is available for further cellular uptake or for cell-surface binding; concentrations in human blood are in the range of 50 nmol/L (Dolealová, 2004). The amount of adenosine present endogenously in humans is several orders of magnitude greater than any exposures resulting from its use as a pesticide inert ingredient; therefore no additional exposure assessment is necessary.

VI. Aggregate Exposures

In examining aggregate exposure, FFDCa section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-

occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in gardens, lawns, or buildings (residential and other indoor uses).

For adenosine, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the extent of its natural presence in all living organisms.

VII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the 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 adenosine 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 adenosine 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 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/>

VIII. Environmental Fate Characterization/Drinking Water Considerations

Adenosine is very water soluble compound, however it is readily degraded in the environment and therefore would not be expected to be present in drinking water sources as a result of its use as a pesticide inert ingredient (EPI Suite, 2004). The estimated chemical fate properties of adenosine are given in Appendix A.

IX. Human Health Risk Characterization

Adenosine is a nucleoside that is essential to the functioning of all living organisms. The available toxicological/pharmacological data available on adenosine do not identify any toxicological concerns associated with exposure to adenosine and the metabolism of adenosine in humans is well understood. Adenosine is readily degraded in the environment, with any potential exposures resulting from the use of adenosine as an inert ingredient being at levels far less than found endogenously in living organisms.

Taking into consideration all available information on adenosine, including the essential role it plays in all living organisms, its well understood synthesis and metabolism, lack of toxicity concerns, and the amounts of adenosine present endogenously in living organisms, it has been

determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to adenosine when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the exemptions from the requirement of a tolerance established for residues of adenosine in/on raw agricultural commodities can be considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

There are no available aquatic toxicity studies on adenosine (ECOTOX, 2002), however, based on estimates of toxicity using physical and chemical property data, adenosine is of low concern for toxicity to fish, algae, and aquatic invertebrates (ECOSAR, 2000). The estimates of ecotoxicity of adenosine are given in Appendix B.

References:

CCRIS. 2005. Chemical Carcinogenesis Research Information System. U.S. National Library of Medicine. National Institutes of Health. Department of Health and Human Services. Online Search Database <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS>
Search term: Adenosine (February 1, 2005)

ChemIDplus. 2005. ChemIDplus Advanced. U.S. National Library of Medicine. National Institutes of Health. Department of Health and Human Services. Online Search Database <http://chem.sis.nlm.nih.gov/chemidplus/>
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Dolealová, P., et al. 2005. Adenosine and Methotrexate Polyglutamate Concentrations in Patients with Juvenile Arthritis Rheumatology. 44(1), pp. 74-79(6). January 2005. Abstract:
<http://www.ingentaconnect.com/content/oup/brheum/2005/00000044/00000001/art00074>

ECOSAR. 2000. Ecological Structure Activity Relationships Version 0.99g. Environmental Protection Agency. <http://www.epa.gov/oppt/newchems/21ecosar.htm>

ECOTOX. 2002. U.S. Environmental Protection Agency. 2002. ECOTOX User Guide: ECOTOXicology Database System. Version 3.0. <http://www.epa.gov/ecotox/>
Search terms: CAS Reg Nos: 58-61-7 (February 2, 2005)

EPI Suite. 2004. Estimation Programs Interface Suite Version 3.12 (August 17, 2004). Environmental Protection Agency. <http://www.epa.gov/opptintr/exposure/docs/episuite.htm>

Mathews, C.K., van Holde, K.E., and Ahern, K.G.. 1999. Biochemistry (3rd Edition). Benjamin Cummings. <http://www.aw-bc.com/mathews/molex/atp.htm>

TOXNET 2005. Hazardous Substance Data Bank (HSDB). On-line Scientific Search Engine,
National Library of Medicine, National Institute of Health. <http://www.toxnet.nlm.nih.gov>.
Search term: Adenosine

APPENDIX A

Physical/Chemical Properties of Adenosine

SMILES : n1cnc2n(C3OC(CO)C(O)C3(O))cnc2c1N

CHEM : Adenosine

CAS NUM: 000058-61-7

MOL FOR: C10 H13 N5 O4

MOL WT : 267.25

----- EPI SUMMARY (v3.12) -----

Physical Property Inputs:

Water Solubility (mg/L): -----

Vapor Pressure (mm Hg) : -----

Henry LC (atm-m³/mole) : -----

Log Kow (octanol-water): -----

Boiling Point (deg C) : -----

Melting Point (deg C) : -----

Log Octanol-Water Partition Coef (SRC):

Log Kow (KOWWIN v1.67 estimate) = -1.38

Log Kow (Exper. database match) = -1.05

Exper. Ref: Hansch,C et al. (1995)

Log Kow (Exper. database match) = -1.11

Exper. Ref: Pomona (1987)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPWIN v1.41):

Boiling Pt (deg C): 537.33 (Adapted Stein & Brown method)

Melting Pt (deg C): 230.04 (Mean or Weighted MP)

VP(mm Hg,25 deg C): 3.29E-015 (Modified Grain method)

MP (exp database): 257-257.5 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.41):

Water Solubility at 25 deg C (mg/L): 8228

log Kow used: -1.11 (expkow database)

no-melting pt equation used

Water Sol Estimate from Fragments:

Wat Sol (v1.01 est) = 1e+006 mg/L

ECOSAR Class Program (ECOSAR v0.99h):

Class(es) found:

Aromatic Amines

Imidazoles

Henry's Law Constant (25 deg C) [HENRYWIN v3.10]:

Bond Method : 1.11E-022 atm-m³/mole

Group Method: Incomplete

Henry's LC [VP/WSol estimate using EPI values]: 1.406E-019 atm-m³/mole

Probability of Rapid Biodegradation (BIOWIN v4.02):

Biowin1 (Linear Model) : 0.5154

Biowin2 (Non-Linear Model) : 0.0590

Expert Survey Biodegradation Results:

Biowin3 (Ultimate Survey Model): 2.9449 (weeks)

Biowin4 (Primary Survey Model) : 3.7324 (days-weeks)

Readily Biodegradable Probability (MITI Model):

Biowin5 (MITI Linear Model) : 0.3599

Biowin6 (MITI Non-Linear Model): 0.0336

Ready Biodegradability Prediction: NO

Atmospheric Oxidation (25 deg C) [AopWin v1.91]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant = 238.3639 E-12 cm³/molecule-sec

Half-Life = 0.045 Days (12-hr day; 1.5E6 OH/cm³)

Half-Life = 0.538 Hrs

Ozone Reaction:

No Ozone Reaction Estimation

Soil Adsorption Coefficient (PCKOCWIN v1.66):

K_{oc} : 10

Log K_{oc}: 1.000

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v1.67]:

Rate constants can NOT be estimated for this structure!

BCF Estimate from Log K_{ow} (BCFWIN v2.15):

Log BCF = 0.500 (BCF = 3.162)

log K_{ow} used: -1.11 (expkow database)

Volatilization from Water:

Henry LC: 1.11E-022 atm-m³/mole (estimated by Bond SAR Method)

Half-Life from Model River: 8.623E+018 hours (3.593E+017 days)

Half-Life from Model Lake : 9.407E+019 hours (3.919E+018 days)

Removal In Wastewater Treatment:

Total removal: 1.85 percent

Total biodegradation: 0.09 percent

Total sludge adsorption: 1.75 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.71e-009	1.08	1000
Water	39	360	1000
Soil	61	720	1000
Sediment	0.0713	3.24e+003	0

Persistence Time: 579 hr

SMILES : n1cnc2n(C3OC(CO)C(O)C3(O))cnc2c1N
CHEM : Adenosine
CAS NUM: 000058-61-7
MOL FOR: C10 H13 N5 O4
MOL WT : 267.25

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Physical Property Inputs:

Water Solubility (mg/L): -----
Vapor Pressure (mm Hg) : -----
Henry LC (atm-m³/mole) : -----
Log Kow (octanol-water): -----
Boiling Point (deg C) : -----
Melting Point (deg C) : -----

Log Octanol-Water Partition Coef (SRC):

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log Kow used: -1.11 (expkow database)
no-melting pt equation used

Water Sol Estimate from Fragments:

Wat Sol (v1.01 est) = 1e+006 mg/L

ECOSAR Class Program (ECOSAR v0.99h):

Class(es) found:
Aromatic Amines
Imidazoles

Henrys Law Constant (25 deg C) [HENRYWIN v3.10]:

Bond Method : 1.11E-022 atm-m3/mole
Group Method: Incomplete

Henrys LC [VP/WSol estimate using EPI values]: 1.406E-019 atm-m3/mole

Probability of Rapid Biodegradation (BIOWIN v4.02):

Biowin1 (Linear Model) : 0.5154
Biowin2 (Non-Linear Model) : 0.0590

Expert Survey Biodegradation Results:

Biowin3 (Ultimate Survey Model): 2.9449 (weeks)
Biowin4 (Primary Survey Model) : 3.7324 (days-weeks)

Readily Biodegradable Probability (MITI Model):

Biowin5 (MITI Linear Model) : 0.3599
Biowin6 (MITI Non-Linear Model): 0.0336

Ready Biodegradability Prediction: NO

Atmospheric Oxidation (25 deg C) [AopWin v1.91]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant = 238.3639 E-12 cm3/molecule-sec
Half-Life = 0.045 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 0.538 Hrs

Ozone Reaction:

No Ozone Reaction Estimation

Soil Adsorption Coefficient (PCKOCWIN v1.66):

Koc : 10
Log Koc: 1.000

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Rate constants can NOT be estimated for this structure!

BCF Estimate from Log Kow (BCFWIN v2.15):

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log Kow used: -1.11 (expkow database)

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Total biodegradation: 0.09 percent

Total sludge adsorption: 1.75 percent

Total to Air: 0.00 percent

(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.71e-009	1.08	1000
Water	39	360	1000
Soil	61	720	1000
Sediment	0.0713	3.24e+003	0

Persistence Time: 579 hr

APPENDIX B

Ecotoxicity of Adenosine

SMILES : n1cnc2n(C3OC(CO)C(O)C3(O))cnc2c1N

CHEM : Adenosine

CAS Num: 000058-61-7

ChemID1:

ChemID2:

ChemID3:

MOL FOR: C10 H13 N5 O4

MOL WT : 267.25

Log Kow: -1.38 (KowWin estimate)

Melt Pt:

Wat Sol: 3.331E+006 mg/L (calculated)

ECOSAR v0.99h Class(es) Found

 Aromatic Amines
 Imidazoles

ECOSAR Class	Organism	Predicted		
		Duration	End Pt	mg/L (ppm)
Neutral Organic SAR (Baseline Toxicity)	: Fish	14-day	LC50	3.15e+005
Aromatic Amines	: Fish	96-hr	LC50	25277.340
Aromatic Amines	: Fish	14-day	LC50	64617.672
Aromatic Amines	: Daphnid	48-hr	LC50	15.062
Aromatic Amines	: Fish		ChV	59.349
Aromatic Amines	: Daphnid		ChV	0.636
Aromatic Amines	: Green Algae		ChV	671.972
Imidazoles	: Fish	96-hr	LC50	10717.941
Imidazoles	: Daphnid	48-hr	LC50	511.483
Imidazoles	: Green Algae	96-hr	EC50	300.491
Imidazoles	: Green Algae	96-hr	ChV	30.820

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Aromatic Amines:

Fish and daphnid acute toxicity log Kow cutoff: 7.0

Green algal EC50 toxicity log Kow cutoff: 7.0

Chronic toxicity log Kow cutoff: 9.0

MW cutoff: 1000

Imidazoles: