

APPENDIX A

**Summary of Available and Relevant Toxicity Data
from Ecological Risk Assessment Literature
Review for Imazapic**

Appendix A

Summary of Available and Relevant Toxicity Data from Ecological Risk Assessment Literature Review for Imazapic

Introduction

A literature review and ecological data evaluation was conducted on nine herbicides that are currently being used or are proposed for use by the Bureau of Land Management (BLM) for vegetation management on 261 million acres of public lands in the Western U.S., including Alaska. The information gathered from this evaluation will be included along with other collected data to derive toxicity reference values for use in the ecological risk assessment (ERA; ENSR 2005). The ERA was conducted in conjunction with the Vegetation Treatments Programmatic Environmental Impact Statement (PEIS) for the BLM. Scientific papers were gathered during this process to provide data on acute and chronic toxicity of selected herbicides to the non-target species. The review process included consideration of U.S. Fish and Wildlife Service (USFWS) draft literature search guidance. The nine herbicides that were investigated during this evaluation were as follows:

- Diflufenzopyr
- Diquat
- Fluridone
- Imazapic
- Sulfometuron-methyl
- Bromacil
- Chlorsulfuron
- Diuron
- Tebuthiuron

This review process was carried out in three tiers: Tier I – Literature search and preliminary review to select individual manuscripts; Tier II – Screening to determine whether the manuscript is acceptable; and Tier III – Thorough review to obtain data for possible toxicity reference value (TRV) use. This report provides information for imazapic; the other chemicals are discussed in separate reports.

Literature Search Methodology

The literature review process was initiated by conducting a keyword search pertaining to each of the nine chemicals in selected databases. The keyword search for all databases, except for one (Chemical Abstracts/Scifinder Scholar), included the herbicide name but not the commercial name (i.e., some commercial names are common words). The search parameters for Chemical Abstracts consisted of the herbicide name and chemical abstracts service (CAS) registry number. The open literature search was conducted at Colorado State University, Fort Collins, CO. The search period for imazapic was from 1970 to 2002. The 12 databases selected and searched were:

- AGRICOLA
- ASFA (Aquatic Sciences and Fisheries Abstracts)
- Biological Sciences
- BIOSIS / Biological Abstracts
- Chemical Abstracts / Scifinder Scholar
- Environmental Science and Pollution Management
- MedLine

- Safety Science and Risk
- Toxline
- Water Resources Abstracts
- Web of Science / Science Citation Index
- Zoological Records

All of the documents obtained in the open literature searches were then evaluated by a Senior Toxicologist to select manuscripts pertaining to the specific objectives of this project (Tier I). Relevant studies were those that were judged, to the extent possible while searching literature databases (i.e., relying on title and abstract, when available), to provide useful data for conducting the ERA. Relevant studies contained the following information at a minimum:

- Acute (mortality vs. survival) or chronic (largely growth or reproduction, although other sublethal data—if available—were also considered potentially relevant) toxicity data for the active ingredient.
- Verifiable numeric endpoint values (e.g., LC₅₀, NOEC) that could be used in the risk characterization process.
- Toxicity data for clinical test species (e.g., mice, rats) and species used for screening non-human impacts (all other mammals, birds, invertebrates, algae, plants).
- Field or mesocosm studies were also included, but only if effects from exposure to the single herbicide in question could be identified and separated from other stressors.

Literature that was excluded as part of this initial literature gathering process included:

- analytical chemistry studies;
- methods papers without specific toxicity data;
- modeling studies that contained no empirically-derived data; and
- reviews or reports that were not primary toxicity data sources (except as a source for obtaining primary literature).

These search criteria enhanced the ability to screen scientific papers for the type of toxicity information needed in the ERA. Hard copies of all manuscripts that met these criteria were then obtained for further evaluation. Once articles were obtained, they were incorporated into a comprehensive management database (EndNote®). There were 243 documents identified from this process and obtained for further consideration. However, no articles were found for imazapic.

Literature Review Methodology

A cursory review (Tier II) was performed on each manuscript after a hard copy was obtained. Exclusion and inclusion criteria to determine acceptability for further review were developed prior to the process in conjunction with the BLM. Manuscripts were excluded that dealt only with the following subjects:

- Human health effects
- Effects on microorganisms: (e.g., fungi, bacteria)
- Genotoxic effects (mutagenic, carcinogenic)
- Bioassays on cells of a whole organism (e.g., rat hepatocytes, rat liver S9)
- Effects on target plants (efficacy testing)
- Non-toxic effects (e.g., fate, transport, leaching, analytical methods)
- Mixtures including herbicides other than the nine being reviewed

In addition, manuscripts that solely included data on marine receptors were originally excluded; however, these data were later included because marine ecosystems could be adjacent to application areas on BLM lands.

Inclusion criteria and rating (on a scale of 1 [weak] to 5 [strong]) of issues that were to be emphasized (requiring a subsequent review step) were as follows:

1. Effects on nontarget receptors related to ERA protocol
2. Chronic, sub-lethal, or reproductive effects that may have adverse effects on populations
3. Effects from inerts, degradates, and metabolites
4. Studies with mixtures that include imazapic and any of the eight other herbicides (i.e., not containing other herbicides)
5. Indirect effects to food supply or cover

Additional criteria that were used in reviewing papers (reviewers answered ‘Yes’ or ‘No’) are listed below:

- Were the corroborating studies described in sufficient detail (i.e., weight of evidence)?
- Did the study have a proper exposure dose, mechanism, and duration?
- Did the test include proper sample size, statistical analysis, and especially statistical endpoints (e.g., NOAEL, EC₅₀) or dose response curves?
- Were proper controls used and were they acceptable?
- Were the data published in a peer-reviewed journal?

Each of the 243 identified papers was scored on the selection criteria listed above, including documentation of the number of test organisms, statistical analysis, proper use, and performance of controls, and the study was classified as either “adequate” or “not adequate.”

In Tier III, papers that were found to be acceptable for use were evaluated more thoroughly based on criteria developed with the BLM, and the following information is included as a second review form page for each manuscript:

- Author(s).
- Date of publication.
- Title of publication.
- Name of publication.
- Herbicide(s) used in the study.
- Receptor category: 20 g mammal, honey bee, 70 kg herbivore, small bird, large bird, non-target plants (monocot and dicot), warmwater fish, coldwater fish, aquatic invertebrate, aquatic plant, aquatic macrophyte). The specific life history stage was also recorded when available.
- Exposure conditions specifying the formulation, concentration, or amount of active ingredient and medium.
- Effect: Acute or sublethal effect end points of product formulations and breakdown products, and/or their component chemicals, such as: larval and embryonic developmental effects, endocrine disruption, reproductive impairment, changes in behavioral traits such as predator avoidance, feeding/appetite, lethargy or excitement, homing ability, swimming speed, or attraction to or repulsion from the chemicals.
- Toxicity endpoints (e.g., NOAEL, EC₅₀, LC₅₀, or dose response curve).
- Degradates, inerts, if available.
- Ecological conditions of study (e.g., mesocosm, static/flow-through, water quality parameters).
- Comments (e.g., mixture effects: additive, synergistic, or antagonistic effect end points of multiple products, other observations).

The Tier II review for imazapic was conducted by only one senior toxicologist, while in the subsequent review process (Tier III), two senior toxicologists independently reviewed papers and determined data adequacy. The

reviews were then compiled, and the pertinent information was entered into a master spreadsheet documenting review findings for possible use in TRV derivation. The documents used in this TRV derivation are designated in **bold** in the bibliography (Appendix A.1), and the derivation of TRVs from all available sources is reported in the ERA (ENSR 2005).

Results

There were no papers discovered in the review of the open literature for imazapic, therefore, there were no papers available for Tier II review or incorporation into the TRV derivation for imazapic (Table 1; Appendix A.2).

TABLE 1
Summary of the Results of the Open Literature Review for Imazapic

Total number of papers obtained for imazapic	0
Total number of papers accepted for Tier II review	0
Total number of papers used in TRV derivation	0

References

ENSR 2005. Imazapic Ecological Risk Assessment Final Report. Prepared for the Bureau of Land Management. February 2005.

APPENDIX A.1
BIBLIOGRAPHY LIST

Appendix A.1. Bibliography List

- American Cyanamid Co. 1997. Letter from L. Miko, Vice President, to U.S. Environmental Protection Agency (USEPA), Office of Pesticide Programs, June 12, as cited in Northwest Coalition for Alternatives to Pesticides (NCAP). 2003. *Journal of Pesticide Reform*. 23(3):10-14.
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- Tu, M., Hurd, C., and J.M. Randall. 2001. *Weed Control Methods Handbook*, The Nature Conservancy, Available at: <http://tncweeds.ucdavis.edu>, Version. April 2001.
- U.S. Environmental Protection Agency (USEPA). 1996. Pesticide Tolerance for Cadre. Final Rule Published in the Federal Register. 40 CFR Part 180.490. Docket number: PP 4F4390/R2215. March 20, 1996.
- _____. 2001. Imazapic; Pesticide Tolerance. Final Rule Published in the Federal Register. 40 CFR Part 180; December 26, 2001. 66 (2471): 66325-66333.
- _____. 2003. USEPA Pesticide Ecotoxicity Database. Provided by Brian Montague, Office of Pesticide Programs. June 6, 2003.

APPENDIX A.2

SPREADSHEET OF TOXICITY DATA FOR IMAZAPIC TRV

Formulation	% purity a.i.	General Taxonomic Group	Common Name	Scientific Name	Age	Test Type	Means of Exposure	Exposure Duration	Test Duration	Biological Endpoint	Statistical Endpoint	Toxicity Value (tested product) ¹	Toxicity Value (ai) ¹	Units	Lab	Study Number	Report Number	Data Source ²	EPA Reviewer	Year of Review	Used for TRV Derivation
Imazapic-ammonium	96.9	terrestrial plants	radish	<i>Rhaphanus sativus</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.0005	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	tomato	<i>Lycopersicon esculentum</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.001	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	cucumber	<i>Cucumis sativus</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.002	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	cabbage	<i>Brassica oleracea</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.001	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	oat	<i>Avena sativa</i>	Juvenile plant			21 d		vegetative vigor	EC ₂₅	NR	0.010	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	oat	<i>Avena sativa</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.004	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	ryegrass	<i>Lolium perenne</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.004	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	corn	<i>Zea mays</i>	Juvenile plant			21 d		vegetative vigor	EC ₂₅	NR	0.020	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	corn	<i>Zea mays</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.016	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	onion	<i>Allium cepa</i>	Juvenile plant			21 d		vegetative vigor	NOEL	NR	0.002	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320309		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	soybean	<i>Glycine max</i>	Seedling			14 d		seed emergence	EC ₂₅	NR	0.040	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	soybean	<i>Glycine max</i>	Seedling			14 d		seed emergence	NOEL	NR	0.032	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	corn	<i>Zea mays</i>	Seedling			14 d		seed emergence	EC₂₅	NR	0.010	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	corn	<i>Zea mays</i>	Seedling			14 d		seed emergence	NOEL	NR	0.004	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	oat	<i>Avena sativa</i>	Seedling			14 d		seed emergence	NOEL	NR	0.004	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	lettuce	<i>Lactuca sativa</i>	Seedling			14 d		seed emergence	NOEL	NR	0.002	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	tomato	<i>Lycopersicon esculentum</i>	Seedling			14 d		seed emergence	NOEL	NR	0.001	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	ryegrass	<i>Lolium perenne</i>	Seedling			14 d		seed emergence	NOEL	NR	0.001	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	onion	<i>Allium cepa</i>	Seedling			14 d		seed emergence	NOEL	NR	0.001	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	radish	<i>Rhaphanus sativus</i>	Seedling			14 d		seed emergence	NOEL	NR	0.0005	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	cucumber	<i>Cucumis sativus</i>	Seedling			14 d		seed emergence	NOEL	NR	0.0005	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	cabbage	<i>Brassica oleracea</i>	Seedling			14 d		seed emergence	NOEL	NR	0.00005	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	Monocots & Dicots (9 sp.)		Seedling			6 d		seed germination	EC ₂₅	NR	> 0.060	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	Monocots & Dicots (9 sp.)		Seedling			6 d		seed germination	NOEL	NR	0.064	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	onion	<i>Allium cepa</i>	Seedling			6 d		seed germination	EC ₂₅	NR	> 0.060	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994 ^{3,4}	A. Yamhure	1995	Yes
Imazapic-ammonium	96.9	terrestrial plants	onion	<i>Allium cepa</i>	Seedling			6 d		seed germination	NOEL	NR	0.032	lb ai/acre	Pan Agricultural Laboratory, CA	MRID 43320308		1994^{3,4}	A. Yamhure	1995	Yes
Imazapic (AC 263,222)		mammal	rabbit			Dermal	Dermal			mortality	LD₅₀	> 2000	NR	mg/kg BW				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	rabbit			Dermal	Dermal	21 d		systemic tox and irritation	NOEL	1000	NR	mg/kg/d				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	rabbit			Dermal	Dermal	21 d		systemic tox and irritation		> 1000	NR	mg/kg/d				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	rat	Sprague-Dawley rat		subchronic	Diet	3 mo			NOEL	20,000 (m: 1,522, f: 1,728)	NR	ppm (mg/kg/d)				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	rat	Sprague-Dawley rat		subchronic	Diet	3 mo				> 20,000 (m: 1,522, f: 1,728)	NR	ppm (mg/kg/d)				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	rat	Sprague-Dawley rat		subchronic	Diet	2 y			NOEL	20,000 (m: 1,029, f: 1,237)	NR	ppm (mg/kg/d)				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	rat	Sprague-Dawley rat		subchronic	Diet	2 y				20,000 (m: 1,029, f: 1,237)	NR	ppm (mg/kg/d)				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	dog	beagle dog		chronic feeding/carcinogenicity	Diet	1 y			NOEL	5000 (m: 137, f: 180)	NR	ppm (mg/kg/d)				USEPA 1996			Yes
Imazapic (AC 263,222)	technical	mammal	dog	beagle dog		chronic feeding/carcinogenicity	Diet	1 y			LOEL	5000 (m: 137; f: 180)	NR	ppm (mg/kg/d)				USEPA 1996			Yes

Formulation	% purity a.i.	General Taxonomic Group	Common Name	Scientific Name	Age	Test Type	Means of Exposure	Exposure Duration	Test Duration	Biological Endpoint	Statistical Endpoint	Toxicity Value (tested product)	Toxicity Value (a.i.) ¹	Units	Lab	Study Number	Report Number	Data Source ²	EPA Reviewer	Year of Review	Used for TRV Derivation
Imazapic		mammal	mouse			chronic feeding	Diet	18 mo			NOEL	7000 (m: 1134; f: 1422)	NR	ppm (mg/kg/d)				USEPA 1996			Yes
Imazapic		mammal	mouse			chronic feeding	Diet	18 mo				7001 (m: 1134; f: 1422)	> NR	ppm (mg/kg/d)				USEPA 1996			Yes
Imazapic (AC 263,222)		mammal	rat	Sprague-Dawley rat		Reproduction	Gavage	gestation days 7 to 19		maternal body weight	NOEL	350	NR	mg/kg/d				USEPA 1996			Yes
Imazapic (AC 263,222)		mammal	rat	Sprague-Dawley rat		Reproduction	Gavage	gestation days 7 to 19		maternal body weight		500	NR	mg/kg/d				USEPA 1996			Yes
Imazapic (AC 263,222)		mammal	rat	Sprague-Dawley rat		Reproduction	Gavage	gestation days 7 to 19		offspring body weight	>	500	NR	mg/kg/d				USEPA 1996			Yes
Imazapic	technical	mammal	rat			Reproduction				maternal	NOEL	1000	NR	mg/kg/d				USEPA 2001			Yes
Imazapic	technical	mammal	rat			Reproduction				developmental	NOEL	1000	NR	mg/kg/d				USEPA 2001			Yes
Imazapic	technical	mammal	rabbit			Reproduction	Gavage			maternal	NOEL	350	NR	mg/kg/d				USEPA 2001			Yes
Imazapic	technical	mammal	rabbit			Reproduction	Gavage			maternal		500	NR	mg/kg/d				USEPA 2001			Yes
Imazapic	technical	mammal	rabbit			Reproduction	Gavage			developmental	NOEL	500	NR	mg/kg/d				USEPA 2001			Yes
Imazapic	technical	mammal	rat			Reproduction				parental	NOEL	1205 (m); 1484 (f)	NR	mg/kg/d				USEPA 2001			Yes
Imazapic	technical	mammal	rat			Reproduction				developmental	NOEL	1205 (m); 1484 (f)	NR	mg/kg/d				USEPA 2001			Yes
Imazapic	technical	mammal	rat			chronic feeding/ carcinogenicity	diet				NOEL	1029 (m); 1237 (f)	NR	mg/kg/d				USEPA 2001			Yes
Imazapic		aquatic invertebrate	water flea	<i>Daphnia magna</i>							EC ₅₀	0.18	NR	mg/L				NCAP 2003			Yes
Imazapic (AC 263,222)	technical	fish	cattfish	<i>Ictalurus punctatus</i>	juvenile	static	Water	96 hr	96 hr	mortality	LC ₅₀	> 100	NR	mg/L	Environmental Science & Engineering, Inc.	MRID 42711436	954-92-120	Yurk et al. 1992 ³			Yes

Boldface indicates study selected for derivation of toxicity reference value (TRV) used in risk assessment.

¹Toxicity values relate the dose of a compound with a potentially adverse effect. Values are reported as they were presented in the reviewed source.

²See Appendix A of the associated Literature Review document for complete citations.

³As cited in USEPA 2003

⁴No author listed

⁵As cited in SERA 2001

Abbreviations

a.i. - active ingredient
 BW - body weight
 CI - confidence interval
 f - female
 m - male
 MRID - Master Record Identification Number
 ppb - parts per billion
 ppm - parts per million
 TRV - Toxicity Reference Value
 ug - micrograms
 NR - Not reported

Endpoints

EC₂₅ - 25% effect concentration
 EC₅₀ - 50% effect concentration
 LC₅₀ - median lethal concentration, 50% mortality
 LD₅₀ - median lethal dose, 50% mortality
 LOEL - lowest observable effect level
 NOEL - no observable effect level
 LOEC - lowest observable effect concentration
 MATC - maximum acceptable toxicant concentration
 NOEC - no observable effect concentration

Durations

hr - hours
 d - days
 w - weeks
 mo - months
 y - years