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TOXIKON FINAL GLP REPORT: 10–0060–G3

HEMOLYSIS – RABBIT BLOOD – ISO DIRECT CONTACT

Test Article
LSR2650

Author
Sulip Goswami, M.S.

Final Report Date
January 13, 2011

COMPLIANCE
21 CFR, Part 58
Good Laboratory Practice for Non–Clinical Laboratory Studies

MANAGEMENT OF THE STUDY

Performing Laboratory
Toxikon Corporation
15 Wiggins Avenue
Bedford, MA 01730

Sponsor
Momentive Perfornance Materials
260 Hudson River Road
Waterford, NY 12188

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STUDY SUMMARY

The test article, LSR2650, exhibited 0.00% hemolysis. The test article is considered non–hemolytic under the experimental conditions employed.

QUALITY ASSURANCE STATEMENT

This study was conducted in compliance with U.S. Food and Drug Administration regulations set forth in 21 CFR, Part 58.

The sections of the regulations not performed by or under the direction of Toxikon Corporation, exempt from this Good Laboratory Practice Statement, included characterization and stability of the test article and its mixture with carriers, 21 CFR, Parts 58.105 and 58.113.

The Quality Assurance Unit conducted inspections on the following dates. The findings were reported to the Study Director and to Toxikon's Management.

INSPECTIONS	DATE OF INSPECTION	DATE REPORTED STUDY DIRECTOR	DATE REPORTED MANAGEMENT
SCORING	01/11/11	01/11/11	01/11/11
RAW DATA	01/13/11	01/13/11	01/13/11
FINAL REPORT	01/13/11	01/13/11	01/13/11

Corrie E. Bergren

Corrie E. Bergren, B.S.
Quality Assurance

1/13/11
Date

STUDY DIRECTOR SIGNATURE AND VERIFICATION DATES

This study meets the technical requirements of the protocol. The study also meets the requirements of the Good Laboratory Practice Regulations, 21 CFR, Part 58, with the exemptions as stated in the Quality Assurance Statement.

Protocol Number:	P10-2335-00A
Study Director:	Sulip Goswami, M.S.
Company:	Toxikon Corporation
Signature:	Sulip Goswami
Date:	1/13/11
Study Supervisor:	Sulip Goswami, M.S.

VERIFICATION DATES:
The Study Initiation Date is the date the protocol is signed by the Study Director.

Test Article Receipt:	11/30/10
Project Log Date:	01/07/11
Study Initiation Date:	01/07/11
Technical Initiation:	01/10/11
Technical Completion:	01/11/11

1.0 PURPOSE

The purpose of the study was to assess the hemolytic activity of the test article in direct contact with rabbit blood.

2.0 REFERENCES

The study was conducted based upon the following references:

2.1 ISO 10993–4, 2002, Biological Evaluation of Medical Devices – Part 4: Selection of Tests for Interactions with Blood, as amended 2006.

2.2 Hemolysis – Rabbit Blood, Evaluation of Hemodialyzers and Dialysis Membranes, DHEW Publication # (NIH) 77–1294, pg. 213, 1977.

2.3 Autian Method, ATTP–I, Material Sciences Toxicology Laboratories, University of Tennessee Center for the Health Sciences, Memphis, TN, April 18, 1977.

2.4 Feldman, Bernard F., Joseph G. Zinkl, and Nemi C. Jain, eds. Schalm's Veterinary Hematology. 5th edition. Baltimore: Lippincott Williams & Wilkins, 2000. 858 – 859.

2.5 ISO 10993–12, 2007, Biological Evaluation of Medical Devices – Part 12: Sample Preparation and Reference Materials.

2.6 ISO/IEC 17025, 2005, General Requirements for the Competence of Testing and Calibration Laboratories.

3.0 COMPLIANCE

The study conformed to the current FDA 21 CFR, Part 58 – Good Laboratory Practice for Non–Clinical Laboratory Studies.

4.0 IDENTIFICATION OF TEST AND CONTROL ARTICLES

The Sponsor supplied the following information on a test requisition form or other correspondence, wherever applicable (excluding confidential or trade secret information). The Sponsor was responsible for all test article characterization data as specified in the GLP regulations.

4.1 Test Article:

Test Article Name: LSR2650
CAS/Code #: Not Supplied by Sponsor (N/S)
Lot/Batch #: ZM6120
Physical State: N/S
Color: N/S

Expiration Date: N/S
Density: N/S
Stability: N/S
Solubility: N/S
pH: N/S
Storage Conditions: Room Temperature
Safety Precautions: Standard Laboratory Safety Precautions
Sponsor Note: Cure Conditions: Press Cured 10 minutes @ 175 C

4.2 Control Articles (Toxikon Supplied):

4.2.1 Negative Control Article Name: USP 0.9% Sodium Chloride for Injection (NaCl)
Toxikon QC #: CSC–10–06–030–CC
Physical State: Liquid
Color: Colorless
Stability: Stable at Room Temperature
Storage Conditions: Room Temperature
Safety Precautions: Standard Laboratory Safety Precautions

4.2.2 Negative Control Article Name: Negative Control High Density Polyethylene (Negative Control Plastic)
Toxikon QC #: CSC–04–05–009–CC
Physical State: Solid
Color: White
Stability: Stable at Room Temperature
Storage Conditions: Room Temperature
Safety Precautions: Standard Laboratory Safety Precautions

4.2.3 Positive Control Article Name: USP Sterile Water for Injection (SWFI)
Toxikon QC #: CSC–10–06–031–CC
Physical State: Liquid
Color: Colorless
Stability: Stable at Room Temperature
Storage Conditions: Room Temperature
Safety Precautions: Standard Laboratory Safety Precautions

5.0 IDENTIFICATION OF TEST SYSTEM

5.1 Animals Used in the Study:

Number and Species: 1 New Zealand White rabbit (*Oryctolagus cuniculus*)

Sex: male

Weight/Age Range: 2.95 kg / at least 7 weeks old (young adult)

Health Status: healthy, previously used in other experimental procedures

Animal Purchase: Robinson Services, Inc., Mocksville, NC

Animal Identification: ear marker

Acclimation: minimum 5 days, prior to the removal of a blood sample

Animal Selection: selected from larger pool and examined to ensure lack of adverse clinical signs

5.2 Animal Care and Maintenance:

Animal Room Temperature: 68 ± 5 °F

Animal Room Relative Humidity: 30–70%

Air Exchanges per Hour: a minimum of 10 changes per hour

Lights: 12–hour light/dark cycle, full spectrum fluorescent lights

Housing: individually housed

Cages: suspended stainless steel

Bedding: hardwood chips, P.W.I. Industries, St. Hyacinthe, Quebec, Canada (non–contact)

Animal Rations: TEK Hi–Fiber Rabbit Diet 2031, Harlan Laboratories, Madison, WI, *ad libitum*

Water: tap water, *ad libitum*

There were no known contaminants present in the feed, water, or bedding expected to interfere with the test data.

The laboratory and animal rooms were maintained as limited–access facilities.

6.0 JUSTIFICATION OF TEST SYSTEM AND ROUTE OF ADMINISTRATION

6.1 The system for the determination of hemolytic activity of a test article, when in direct contact with rabbit blood, is recommended in the DHEW Publication, Evaluation of Hemodialyzers and Dialysis Membranes. The guidelines have no alternative (non–animal) methods.

6.2 The system for the determination of hemolytic activity of a test article when in direct contact with rabbit blood is designed to simulate the conditions of the use of the test article. Evaluation of blood compatibility is a significant screening test because elevated plasma hemoglobin levels reflect red blood cell lysis upon direct contact with material and devices and is a requirement to assess effects on blood, per ISO 10993–4 guidelines.

6.3 The test article was administered *in vitro*, directly to the test system. The route of administration was recommended by the references in Section 2.0.

7.0 EXPERIMENTAL DESIGN AND DOSAGE

7.1 Pre–Dose Procedure:

7.1.1 Blood Sample:
Fresh, whole rabbit blood was collected into EDTA–coated vacutainer tubes and was utilized within four hours of collection. It was diluted sufficiently in NaCl until 0.2 mL was hemolyzed in 10 mL of SWFI and the spectrophotometric reading at 545 nm was approximately 1.0 Absorbance unit (A).

7.1.2 The test article (5 g) was added to three test vials containing 10 mL of NaCl at a ratio of 5 g test article per 10 mL of NaCl.

7.1.3 Negative Control Article:
The Negative Control Plastic was added to three vials containing NaCl at a ratio of 3 cm^2 per 1 mL of NaCl.

7.1.4 Positive Control Article:
A volume of 10 mL of SWFI was added to each positive control vial.

7.1.5 Untreated Control Article:
A volume of 10 mL of NaCl was added to each untreated control vial.

7.2 Dose Administration:

7.2.1 Addition of Blood:
All vials were incubated in a 37 ± 2 °C water bath for at least 30 minutes to equilibrate the temperature. Diluted blood, prepared as reported in Section 7.1.1, was added to each vial at a ratio of 0.2 mL diluted blood per 10 mL.

7.2.2 Replication:
The test article, as well as the positive and negative controls, were tested in triplicate.

7.3 Post–Dose Procedure:

7.3.1 All vials were incubated in a 37 ± 2 °C water bath for 60 ± 4 minutes. After incubation, the vials were centrifuged for five minutes at approximately 750 x *g*.

7.3.2 Absorbance of each supernatant was determined against a NaCl blank at 545 nm.

8.0 EVALUATION CRITERIA

8.1 The average absorbance values are used to determine the percent (%) Hemolysis of the test article according to the following calculation.

$$\% \text{ Hemolysis} = \frac{\text{Abs. of Test Article} - \text{Abs. of Untreated Control}}{\text{Abs. of Positive Control} - \text{Abs. of Untreated Control}} \times 100$$

The average absorbance values are used to determine the percent (%) Hemolysis of the negative control according to the following calculation.

$$\% \text{ Hemolysis} = \frac{\text{Abs. of Negative Control} - \text{Abs. of Untreated Control}}{\text{Abs. of Positive Control} - \text{Abs. of Untreated Control}} \times 100$$

8.2 The test article is considered hemolytic if it causes greater than 5% hemolysis.

8.3 The test is considered invalid if the % hemolysis of the negative control was greater than 2% hemolysis.

8.4 If deemed necessary by the Study Director, a retest is performed using fresh blood from the same donor and a new test article.

8.5 The study and its design employ methodology to minimize uncertainty of measurement and control of bias for data collection and analysis.

9.0 RESULTS

TABLE 1
Absorbance at 545 nm

Tube	Test Article	Positive Control	Negative Control	Untreated Control
1	0.0149	0.9260	0.0186	0.0160
2	0.0165	0.8895	0.0193	0.0195
3	0.0194	0.9078	0.0179	0.0161
Average Absorbance	**0.0169**	**0.9078**	**0.0186**	**0.0172**

Test Article Hemolysis = 0.00%

Negative Control Hemolysis = 0.16%

10.0 CONCLUSION

The test article, LSR2650, exhibited 0.00% hemolysis. The test article is considered non–hemolytic under the experimental conditions employed.

11.0 RECORDS

11.1 Original raw data are archived at Toxikon Corporation.

11.2 A copy of the final report and any report amendments is archived at Toxikon Corporation.

11.3 The original final report, and a copy of any protocol amendments or deviations, is forwarded to the Sponsor.

11.4 All used and unused test article shall be disposed of by Toxikon.

12.0 CONFIDENTIALITY AGREEMENT

Per corporate policy, confidentiality shall be maintained in general, and in specific accordance with any relevant agreement specifically executed between Toxikon and the Sponsor.

13.0 ANIMAL WELFARE STATEMENT

The Sponsor assured that, to the best of their knowledge, this study did not unnecessarily duplicate previous testing and that there were no non–animal alternatives acceptable for the evaluation of this test article as defined by the protocol.

No evidence of pain and suffering was reported to the Veterinarian and/or Study Director.

Toxikon strictly adhered to the following standards in maintaining the animal care and use program:

United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service, 9 CFR Ch. 1 (1/1/95 edition), Subchapter A–Animal Welfare.

"Guide for the Care and Use of Laboratory Animals," National Research Council, 1996. (NIH).

Office for Laboratory Animal Welfare (OLAW), "Public Health Service Policy on Humane Care and Use of Laboratory Animals," Health Research Extension Act of 1985 (Public Law 99–158 November 20, 1985), Reprinted 1996.

ISO 10993–2, 2006, Biological Evaluation of Medical Devices – Part 2: Animal Welfare Requirements.

Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

APPENDIX I
Software Systems

Software	Use
Adobe Acrobat 8 Professional	Document preparation
DocuKnowledge 3.0	Lotus Domino–based document management system used for SOPs
Lotus Domino Rel. 5	Client–server application for sponsor, sample, test codes, and quotation management application databases
MS Office 2007 Small Business Suite	Business software (suite includes Word, Excel, PowerPoint, Outlook, Publisher, Office tools)
Rees CentronSQL System 2.0	Environmental monitoring and metrology system
UV_WINLAB V.2.85.04	Spectrophotometer for absorption measurement

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TOXIKON TEST PROTOCOL
FDA GLP REGULATIONS
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HEMOLYSIS – RABBIT BLOOD – ISO

TOXIKON PROTOCOL NUMBER: P10–2335–00A

COMPLIANCE
21 CFR, Part 58
Good Laboratory Practice for Non–Clinical Laboratory Studies

MANAGEMENT OF THE STUDY

Performing Laboratory
Toxikon Corporation
15 Wiggins Avenue
Bedford, MA 01730

Sponsor
Momentive Performance Materials
260 Hudson River Road
Waterford, NY 12188

ORIGINAL

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PROTOCOL ACCEPTANCE

SHAHZAD ARSHAD
PRINT NAME

Sponsor's Representative Signature — Date: 1-6-11
Momentive Performance Materials
260 Hudson River Road
Waterford, NY 12188

Corrie E. Bergen
PRINT NAME

Quality Assurance Signature — Date: 1/6/11
Toxikon Corporation
15 Wiggins Avenue
Bedford, MA 01730

SULIP GOSWAMI
PRINT NAME

Study Director Signature — Date: 1/7/11
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Bedford, MA 01730

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1.0 PURPOSE

The purpose of the study is to assess the hemolytic activity of a test article in direct or indirect contact with rabbit blood.

2.0 REFERENCES

The study will be based upon the following references:

2.1 ISO 10993–4, 2002, Biological Evaluation of Medical Devices – Part 4: Selection of Tests for Interactions with Blood, as amended 2006.

2.2 Hemolysis – Rabbit Blood, Evaluation of Hemodialyzers and Dialysis Membranes, DHEW Publication # (NIH) 77–1294, pg. 213, 1977.

2.3 Autian Method, ATTP–I, Material Sciences Toxicology Laboratories, University of Tennessee Center for the Health Sciences, Memphis, TN, April 18, 1977.

2.4 Feldman, Bernard F., Joseph G. Zinkl, and Nemi C. Jain, eds. Schalm's Veterinary Hematology. 5th edition. Baltimore: Lippincott Williams & Wilkins, 2000. 858–859.

2.5 ISO 10993–12, 2007, Biological Evaluation of Medical Devices – Part 12: Sample Preparation and Reference Materials.

2.6 ISO/IEC 17025, 2005, General Requirements for the Competence of Testing and Calibration Laboratories.

3.0 COMPLIANCE

The study will conform to the current FDA 21 CFR, Part 58 – Good Laboratory Practice for Non–Clinical Laboratory Studies.

4.0 IDENTIFICATION OF TEST AND CONTROL ARTICLES

The Sponsor will supply the following information on a test requisition form or other correspondence, wherever applicable (excluding confidential or trade secret information). The Sponsor will be responsible for all test article characterization data as specified in the GLP regulations. Test and control articles (exclusive of extracts) that are mixed with carriers require verification of concentration, homogeneity, and stability. Samples of test and control article mixtures will be returned to the Sponsor for characterization and verification, unless this work was specifically contracted to Toxikon by Sponsor under a separate analytical protocol, whichever is applicable.

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4.1 Test Article:

Test Article Name: To Be Determined (TBD)
CAS/Code #: TBD
Lot/Batch #: TBD
Physical State: TBD
Color: TBD
Expiration Date: TBD
Density: TBD
Stability: TBD
Solubility: TBD
pH: TBD
Storage Conditions: TBD
Safety Precautions: TBD

4.2 Control Article(s) (Toxikon Supplied, unless specified by the Sponsor):

4.2.1 Negative Control Article Name: USP 0.9% Sodium Chloride for Injection (NaCl)
Toxikon QC #: To Be Determined (TBD)
Physical State: Liquid
Color: Colorless
Stability: Stable at Room Temperature
Storage Conditions: Room Temperature
Safety Precautions: Standard Laboratory Safety Precautions

4.2.2 Negative Control Article Name: Negative Control High Density Polyethylene (Negative Control Plastic)
Toxikon QC #: To Be Determined (TBD)
Physical State: Solid
Color: White
Stability: Stable at Room Temperature
Storage Conditions: Room Temperature
Safety Precautions: Standard Laboratory Safety Precautions

4.2.3 Positive Control Article Name: USP Sterile Water for Injection (SWFI)
Toxikon QC #: To Be Determined (TBD)
Physical State: Liquid
Color: Colorless
Stability: Stable at Room Temperature
Storage Conditions: Room Temperature
Safety Precautions: Standard Laboratory Safety Precautions

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5.0 IDENTIFICATION OF TEST SYSTEM

5.1 Animals Used in the Study:

Number and Species: 1 New Zealand White rabbit (*Oryctolagus cuniculus*)

Sex: male or female (female will be non–pregnant and nulliparous)

Weight/Age Range: at least 1.70 kilograms / at least 7 weeks old (young adult) weighed to the nearest 10 g

Health Status: healthy, may be previously used in other experimental procedures

Animal Purchase: registered commercial breeder

Animal Identification: ear tattoo or ear marker

Acclimation: minimum 5 days, prior to the removal of a blood sample

Animal Selection: selected from larger pool and examined to ensure lack of adverse clinical signs

5.2 Animal Care and Maintenance:

Animal Room Temperature: 68 ± 5 °F

Animal Room Relative Humidity: 30–70%

Air Exchanges per Hour: a minimum of 10 changes per hour

Lights: 12–hour light/dark cycle, full spectrum fluorescent lights

Housing: individually housed

Cages: suspended stainless steel

Bedding: laboratory grade bedding used as non–contact bedding

Animal Rations: commercial rabbit ration, *ad libitum*

Water: tap water, *ad libitum*

There will be no known contaminants present in the feed, water, or bedding expected to interfere with the test data.

The laboratory and animal rooms are maintained as limited–access facilities.

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6.0 JUSTIFICATION OF TEST SYSTEM AND ROUTE OF ADMINISTRATION

6.1 The system for the determination of hemolytic activity of a test article, when in direct or indirect contact with rabbit blood, is recommended in the DHEW Publication, Evaluation of Hemodialyzers and Dialysis Membranes. The guidelines have no alternative (non–animal) methods.

6.2 The system for the determination of hemolytic activity of a test article when in direct or indirect contact with rabbit blood is designed to simulate the conditions of the use of the test article. Evaluation of blood compatibility is a significant screening test because elevated plasma hemoglobin levels reflect red blood cell lysis upon direct or indirect contact with material and devices and is a requirement to assess effects on blood, per the ISO 10993–4 guidelines.

6.3 The test article will be administered *in vitro*, directly or through a solvent compatible with the test system. The route of administration is recommended by the references in Section 2.0.

7.0 EXPERIMENTAL DESIGN AND DOSAGE

7.1 Preparation of Test and Negative Control Articles for Indirect Contact Testing (Extracts):

7.1.1 The test article extract will be prepared at the following ratios (please indicate on the test requisition form):

1. Specified by the Sponsor
2. No preparation required
3. According to ISO 10993–12

7.1.2 The test article extract will be prepared with the following media (please indicate on the test requisition form):

1. USP 0.9% Sodium Chloride for Injection (NaCl)
2. Sponsor–specified medium

7.1.3 Extraction conditions will be determined by the Sponsor from one of the following choices (please indicate on the test requisition form):

1. 37 ± 1 °C for 72 ± 2 hours
2. 50 ± 2 °C for 72 ± 2 hours
3. 70 ± 2 °C for 24 ± 2 hours
4. 121 ± 2 °C for 1 ± 0.1 hour
5. Sponsor–specified

7.1.4 Properly prepared test articles will be placed in separate extraction bottles and to each bottle the appropriate medium will be added. The extraction medium should completely cover the test article.

7.1.5 The negative control article will be prepared in the same manner as the test article at a ratio of 3 cm^2/1 mL.

7.1.6 Each extract will be agitated vigorously prior to administration. All other test article preparation will be as specified by the Sponsor.

7.1.7 The pH of the extract may be evaluated.

7.1.8 The absorbance of the extract may be measured before addition of blood.

7.2 Pre–Dose Procedure:

7.2.1 Blood Sample:
Fresh, whole rabbit blood will be collected into EDTA–coated vacutainer tubes and will be used for testing within four hours of collection. The blood will be diluted sufficiently in NaCl until 0.2 mL of blood hemolyzes in 10 mL of USP Sterile Water for Injection (SWFI) and gives a spectrophotometric reading of approximately 1.0 Absorbance unit (A) at 540–545 nm.

7.2.2 Test by Direct Contact:

7.2.2.1 The test article will be added to three test vials containing NaCl at a ratio of 5 g test article per 10 mL of NaCl. For low density test articles which cannot be submerged in NaCl, the test article will be tested at a ratio of 0.5 g of test article per 10 mL of NaCl. Alternately, an exposure ratio by surface area, as defined by ISO 10993–12, can be used per Sponsor request.

7.2.2.2 Liquid test articles will be dosed as per Sponsor specifications.

7.2.2.3 Negative Control Article:
The Negative Control Plastic will be added to three vials containing NaCl at a ratio of 3 cm^2 per 1 mL of NaCl.

7.2.2.4 Positive Control Article:
A volume of 10 mL of SWFI will be added to each positive control vial.

7.2.2.5 Untreated Control:
A volume of 10 mL of NaCl will be added to each untreated control vial.

7.2.3 Test by Indirect Contact (Extract):

7.2.3.1 10 mL of test article extract will be added to each test vial. A smaller volume of extract may be used in case of test article scarcity.

7.2.3.2 10 mL of negative control extract will be added to each test vial.

7.2.3.3 Positive Control Article:
A volume of 10 mL of SWFI will be added to each positive control vial.

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7.2.3.4 Untreated Control:
A volume of 10 mL of NaCl will be added to each untreated control vial.

7.3 Dose Administration:
All vials prepared as indicated in Section 7.2.2 and/or 7.2.3 will be incubated in a 37 ± 2 °C water bath for at least 30 minutes to equilibrate the temperature.

The diluted blood prepared as indicated in Section 7.2.1 will be added to each vial at a ratio of 0.2 mL per 10 mL.

7.4 Post–Dose Procedure:

7.4.1 All vials will be incubated in a 37 ± 2 °C water bath for 60 ± 4 minutes with gentle agitation.

7.4.2 After incubation, the vials will be centrifuged for five minutes at approximately 500–750 x *g*.

7.4.3 Absorbance of each supernatant will be determined against a NaCl blank at 540–545 nm on a calibrated spectrophotometer.

8.0 EVALUATION CRITERIA

8.1 The average absorbance values will be used to determine the percent (%) hemolysis of the test article according to the following calculation:

$$\% \text{ Hemolysis} = \frac{\text{Abs. of Test Article} - \text{Abs. of Untreated Control}}{\text{Abs. of Positive Control} - \text{Abs. of Untreated Control}} \times 100$$

The average absorbance values will be used to determine the percent (%) hemolysis of the negative control according to the following calculation:

$$\% \text{ Hemolysis} = \frac{\text{Abs. of Negative Control Article} - \text{Abs. of Untreated Control}}{\text{Abs. of Positive Control} - \text{Abs. of Untreated Control}} \times 100$$

8.2 The test article will be considered hemolytic if it causes greater than 5% hemolysis.

8.3 The test will be considered invalid if the % hemolysis of the negative control is greater than 2% hemolysis.

8.4 If deemed necessary by the Study Director, a retest will be performed using fresh blood from the same donor and a new test article.

8.5 The study and its design will employ methodology to minimize uncertainty of measurement and control of bias for data collection and analysis.

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9.0 RECORDS

9.1 Original raw data will be archived at Toxikon Corporation.

9.2 A copy of the final report and any report amendments will be archived at Toxikon Corporation.

9.3 The original final report, and a copy of any protocol amendments or deviations, will be forwarded to the Sponsor.

9.4 All unused test article will be handled as specified on the Test Requisition Form. If not indicated on the Test Requisition Form, all remaining test article will be discarded.

10.0 CONFIDENTIALITY AGREEMENT

Per corporate policy, confidentiality shall be maintained in general, and in specific accordance with any relevant agreement specifically executed between Toxikon and the Sponsor.

11.0 ANIMAL WELFARE STATEMENT

The Sponsor assures that, to the best of their knowledge, this study does not unnecessarily duplicate previous testing and that there are no non–animal alternatives acceptable for the evaluation of the test article as defined by the protocol.

Evidence of pain and distress will be immediately reported to the Veterinarian and/or Study Director, who will make a decision, independently or in consent with the Sponsor, to terminate the study or to continue with or without appropriate analgesics. In toxicity studies, animals cannot be administered analgesics since they would interfere with the toxicity determination. Animals may be immediately euthanized. In other studies, one or more analgesics may be administered to reduce pain and distress. The Institutional Official and the Animal Care and Use Committee (IACUC) base this policy upon Toxikon's Standard Operating Procedures and animal care and welfare standards as governed.

Toxikon strictly adheres to the following standards, where applicable, in maintaining the animal care and use program:

United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service, 9 CFR Ch. 1 (1/1/95 edition), Subchapter A–Animal Welfare.

"Guide for the Care and Use of Laboratory Animals," National Research Council, 1996. (NIH).

Office for Laboratory Animal Welfare (OLAW), "Public Health Service Policy on Humane Care and Use of Laboratory Animals," Health Research Extension Act of 1985 (Public Law 99–158 November 20, 1985), Reprinted 1996.

ISO 10993–2, 2006, Biological Evaluation of Medical Devices – Part 2: Animal Welfare Requirements.

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Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International.

12.0 PROTOCOL AMENDMENTS/DEVIATIONS

All changes to the approved protocol and the reason for the changes will be documented in writing, signed by the Study Director, dated, and maintained with the protocol. A Protocol Amendment/Deviation Report (PADR) will be generated as closely as possible to the time of the change. The document will be created and signed by the Study Director and sent to the Sponsor. Sponsor's signature will be required for amendments to indicate approval of the amendment. Acknowledgement of notification of deviations will either be with a signature or other form of documentation.

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APPENDIX I
Software Systems

The following are the proposed software systems to be used during the conduct of this study. The actual systems used will be documented in the final report.

Software	Use
Adobe Acrobat 8 Professional	Document preparation
DocuKnowledge 3.0	Lotus Domino–based document management system used for SOPs
Lotus Domino Rel. 5	Client–server application for sponsor, sample, test codes, and quotation management application databases
MS Office 2007 Small Business Suite	Business software (suite includes Word, Excel, PowerPoint, Outlook, Publisher, Office tools)
Rees CentronSQL System 2.0	Environmental monitoring and metrology system
UV_WINLAB V.2.85.04	Spectrophotometer for absorption measurement