[redacted]

[redacted]

April 14, 2015

CONFIDENTIAL

4/29/15

Office of Pollution Prevention
and Toxic Substances
U.S. E.P.A.
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Attn: Geraldine Hilton

Re: Original Signed Consent Order
EPA Ref: P-11-0150 [redacted]

Dear Ms. Hilton:

Further to our telephone conversation earlier today, attached please find an original signed consent order for the above-identified matter, including pages iii and 4 that you previously sent to me by facsimile.

If you have any questions, please let me know.

[redacted]

[redacted]

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF POLLUTION PREVENTION AND TOXICS

REGULATION OF A NEW CHEMICAL SUBSTANCE

PENDING DEVELOPMENT OF INFORMATION

In the matter of:	)	Premanufacture Notice Number:
	)	
	)	
	)	
	)	
	)	
[redacted]	)	P-11-150
	)	
	)	
	)	
	)	
	)	

~~TSCA CONFIDENTIAL BUSINESS INFORMATION DOES NOT CONTAIN NATIONAL SECURITY INFORMATION (E.O. 12065)~~

Consent Order and Determinations Supporting Consent Order

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PREAMBLE

I. INTRODUCTION

Under the authority of § 5(e) of the Toxic Substances Control Act ("TSCA") (15 U.S.C. 2604(e)), the Environmental Protection Agency ("EPA" or "the Agency") issues the attached Order, regarding premanufacture notice ("PMN") P-11-150 for the chemical substance [redacted] ("the PMN substance") submitted by [redacted] ("the Company"), to take effect upon expiration of the PMN review period. The Company submitted the PMN to EPA pursuant to § 5(a)(1) of TSCA and 40 CFR Part 720.

Under § 15 of TSCA, it is unlawful for any person to fail or refuse to comply with any provision of § 5 or any order issued under § 5. Violators may be subject to various penalties and to both criminal and civil liability pursuant to § 16, and to specific enforcement and seizure pursuant to § 17. In addition, chemical substances subject to an Order issued under § 5 of TSCA, such as this one, are subject to the § 12(b) export notice requirement.

II. SUMMARY OF TERMS OF THE ORDER

The Consent Order for this PMN substance requires the Company to:

(a) submit to EPA certain toxicity testing before manufacturing (which includes import) a total of [redacted] kilograms of the PMN substance;

(b) provide respirators to its workers to prevent inhalation exposure;

(c) as an alternative to using respirators, maintain workplace airborne concentrations of the PMN substance at or below a specified New Chemical Exposure Limit ("NCEL") of 2.4 mg/m^3 as a 8-hour time weighted average, verified by actual exposure monitoring data (to pursue this

option, a sampling and analytical method must be developed by the Company, verified by an independent third-party laboratory, and submitted to EPA);

(d) label containers of the PMN substance and provide Material Safety Data Sheets ("MSDSs") and worker training in accordance with the provisions of the Hazard Communication Program section;

(e) distribute the PMN substance only to a person who agrees to follow the same restrictions (except the testing requirements) and to not further distribute the PMN substance until it has been completely reacted; and

(f) maintain certain records.

v

III. CONTENTS OF PMN

By signing this Order, the Company represents that it has carefully reviewed this document and agrees that all information herein that is claimed as confidential by the Company is correctly identified within brackets and that any information that is not bracketed is not claimed as confidential. To make this document available for public viewing, EPA will remove only the information contained within the brackets.

Confidential Business Information Claims (Bracketed in the Preamble and Order): Company name, chemical identity, use information and production volume.

Chemical Identity:

Specific: [redacted]

Generic: Alkali transition metal oxide

Use:

Specific: [redacted]]

Generic: Battery materials

Maximum 12-Month Production Volume: [redacted]]

Test Data Submitted with PMN: Chromosomal Aberration Test of [redacted] using cultured mammalian cells; Homogeneity, Stability and Concentration Analysis of [redacted] formulation; Mutagenicity Test of [redacted] using microorganisms; and 28-Day Repeated Dose Oral Toxicity study of [redacted] in rats

IV. EPA'S ASSESSMENT OF EXPOSURE AND RISK

The following are EPA's predictions regarding the probable human and environmental toxicity, human exposure and environmental release of the PMN substance, based on the information currently available to the Agency.

Human Health Effects Summary:

Absorption: Not absorbed through the skin, poor absorption from the lung and GI tract.

Toxicological Endpoints of Concern: Lung toxicity, blood toxicity, adrenal gland toxicity, neurotoxicity, developmental toxicity, developmental neurotoxicity, cardiovascular effects, gastrointestinal effects, immunosuppression, and kidney toxicity.

Basis: Based on submitted test data and data on titanium dioxide.

See www.epa.gov/opptintr/newchems/pubs/chemcat.htm

Environmental Effects Summary: No effects at saturation.

Exposure Summary:

	Use
# Sites	[redacted]
Workers (#/site)	[redacted]
Exposure (days/year)	[redacted]
Inhalation Exposure (mg/day)	120

Risk to Workers: Concern for lung toxicity if inhaled based on lung overload for poorly soluble particulates (particle size range 5 - 50μm); mutagenicity based on submitted test data and data for titanium dioxide; blood and adrenal gland toxicity (at 1000 mg/kg) based on submitted test data. Also concern for neurotoxicity, developmental toxicity (NOEL = 14 mg Li/kg/d),

developmental neurotoxicity, cardiovascular effects, GI effects, immunosuppression, and kidney toxicity from the Li (to the extent lithium is bioavailable);the dose respone curve for Li is very steep. Concern for hypersensitivity based on titanium dioxide.

NIOSH Assigned Protection Factor ("APF"): 10

New Chemical Exposure Limit: 2.4 mg/m^3 as an 8-hour time-weighted average ("TWA") based on the current Draft NIOSH REL.

V. EPA'S CONCLUSIONS OF LAW

The following findings constitute the basis of the Consent Order:

(a) EPA is unable to determine the potential for human health effects from exposure of humans to the PMN substance. EPA therefore concludes, pursuant to § 5(e)(1)(A)(i) of TSCA, that the information available to the Agency is insufficient to permit a reasoned evaluation of the human health and environmental effects of the PMN substance.

(b) In light of the potential risk of human health effects posed by the uncontrolled manufacture (which includes import), processing, distribution in commerce, use, and disposal of the PMN substance, EPA has concluded, pursuant to § 5(e)(1)(A)(ii)(I) of TSCA, that uncontrolled manufacture (which includes import), processing, distribution in commerce, use, and disposal of the PMN substance may present an unreasonable risk of injury to human health.

VI. INFORMATION REQUIRED TO EVALUATE HUMAN HEALTH AND ENVIRONMENTAL EFFECTS

Triggered Testing. The Order prohibits the Company from exceeding a specified production volume unless the Company submits the information described in the Testing section of this Order in accordance with the conditions specified in the Testing section.

Pended Testing. The following additional information would be required to evaluate the following effects which may be caused by the PMN substance:

Information	Effects	Guidelines
2-year Inhalation Bioassay	Oncogenicity	OSCPP 870.4200

The Order does not require submission of the above pended testing at any specified time or production volume. However, the Order's restrictions on manufacture (which includes import), processing, distribution in commerce, use, and disposal of the PMN substance will remain in effect until the Order is modified or revoked by EPA based on submission of that or other relevant information.

CONSENT ORDER

I. SCOPE OF APPLICABILITY AND EXEMPTIONS

(a) Scope. The requirements of this Order apply to all commercial manufacturing, processing, distribution in commerce, use and disposal of the chemical substance [redacted] (P-11-150)("the PMN substance") in the United States by [redacted] ("the Company"), except to the extent that those activities are exempted by paragraph (b).

(b) Exemptions. Manufacturing (which includes import), processing, distribution in commerce, use and disposal of the PMN substance is exempt from the requirements of this Order (except the requirements in the Recordkeeping and Successor Liability Upon Transfer Of Consent Order sections) only to the extent that (1) these activities are conducted in full compliance with all applicable requirements of the following exemptions, and (2) such compliance is documented by appropriate recordkeeping as required in the Recordkeeping section of this Order.

(1) Export. Until the Company begins commercial manufacture (which includes import) of the PMN substance for use in the United States, the requirements of this Order do not apply to manufacture (which includes import), processing or distribution in commerce of the PMN substance solely for export in accordance with TSCA §§12(a) and 12(b), 40 CFR 720.3(s) and 40 CFR Part 707. However, once the Company begins to manufacture (which includes import) the PMN substance for use in the United States, no further activity by the Company involving the PMN substance is exempt as "solely for export" even if some amount of the PMN substance is later exported. At that point, the requirements of this Order apply to all activities associated with the PMN substance while in the territory of the United States. Prior to leaving U.S. territory, even those quantities or batches of the PMN substance that are destined for export are subject to terms of the Order, and count towards any production volume test triggers in the Testing section of this Order.

(2) Research & Development ("R&D"). The requirements of this Order do not apply to manufacturing (which includes import), processing, distribution in commerce, use and disposal of the PMN substance in small quantities solely for research and development in accordance with TSCA §5(h)(3), 40 CFR 720.3(cc), and 40 CFR 720.36. The requirements of this Order also do not apply to manufacturing, processing, distribution in commerce, use and disposal of the PMN substance when manufactured (which includes import) solely for non-commercial research and development per TSCA §5(i) and 40 CFR 720.30(i).

(3) Byproducts. The requirements of this Order do not apply to the PMN substance when it is produced, without separate commercial intent, only as a "byproduct" as defined at 40 CFR 720.3(d) and in compliance with 40 CFR 720.30(g).

(4) No Separate Commercial Purpose. The requirements of this Order do not apply to the PMN substance when it is manufactured (which includes import), pursuant to any of the exemptions in 40 CFR 720.30(h), with no commercial purpose separate from the substance, mixture, or article of which it is a part.

(5) Imported Articles. The requirements of this Order do not apply to the PMN substance when it is imported as part of an "article" as defined at 40 CFR 720.3(c) and in compliance with 40 CFR 720.22(b)(1).

(6) Completely Reacted (Cured). The requirements of this Order do not apply to quantities of the PMN substance after they have been completely reacted (cured).

(c) Automatic Sunset. If the Company has obtained for the PMN substance a Test Market Exemption ("TME") under TSCA §5(h)(1) and 40 CFR 720.38 or a Low Volume Exemption ("LVE") or Low Release and Exposure Exemption ("LoREX") under TSCA §5(h)(4) and 40 CFR 723.50(c)(1) and (2) respectively, any such exemption is automatically rendered null and void as of the effective date of this Consent Order.

II. TERMS OF MANUFACTURE (WHICH INCLUDES IMPORT), PROCESSING, DISTRIBUTION IN COMMERCE, USE, AND DISPOSAL PENDING SUBMISSION AND EVALUATION OF INFORMATION

PROHIBITION

The Company is prohibited from manufacturing (which includes import), processing, distributing in commerce, using, or disposing of the PMN substance in the United States, for any nonexempt commercial purpose, pending the development of information necessary for a reasoned

evaluation of the human health of the substance, and the completion of EPA's review of, and regulatory action based on, that information, except in accordance with the conditions described in this Order.

TESTING

(a) Section 8(e) Reporting. Reports of information on the PMN substance which reasonably supports the conclusion that the PMN substance presents a substantial risk of injury to health or the environment and which is required to be reported under TSCA section 8(e) shall reference the appropriate PMN identification number for this substance and contain a statement that the substance is subject to this Consent Order. Additional information regarding section 8(e) reporting requirements can be found at *www.epa.gov/oppt/tsca8e*.

(b) Notice of Study Scheduling. The Company shall notify, in writing, the EPA Monitoring Assistance and Media Programs Division (2227A), Office of Enforcement and Compliance Assurance, U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, N.W., Washington, D.C. 20460, of the following information within 10 days of scheduling any study required to be performed pursuant to this Order, or within 15 days after the effective date of this Order, whichever is later:

(1) The date when the study is scheduled to commence;

(2) The name and address of the laboratory which will conduct the study;

(3) The name and telephone number of a person at the Company or the laboratory whom EPA may contact regarding the study; and,

(4) The appropriate PMN identification number for each substance and a statement that the substance is subject to this Consent Order.

(c) Good Laboratory Practice Standards and Test Protocols. Each study performed to address the risks identified in this Order must be conducted according to TSCA Good Laboratory Practice Standards at 40 CFR Part 792 and using methodologies generally accepted in the relevant scientific community at the time the study is initiated. Before starting to conduct any study that will use a modified version of a published test guideline, the Company must submit written test protocols to EPA for review (submission of written test protocols is optional for tests that are to be conducted using unmodified published test guidelines). Protocols must be submitted as a support document for the PMN, using the procedures set out in 40 CFR 720.40. EPA will respond to the Company within 4 weeks of receiving the written protocols. EPA review of a test protocol does not mean pre-acceptance of test results.

(d) Triggered Testing Requirements. The Company is prohibited from manufacturing (which includes import) the PMN substance after a certain aggregate manufacture (which includes import) volume ("the production limit"), unless the Company conducts the following studies on the PMN substance and submits all final reports and underlying data in accordance with the conditions specified in this Testing section.

Production Limit	Study	Test Guideline
[redacted]	90-day Inhalation Toxicity Study with special attention to histopathology (inflammation and cell proliferation) of the lung tissues and various parameters	OPPTS 870.3465

of the bronchoalveolar lavage fluid (BALF) e.g., maker enzyme activities, total protein content, total cell count, cell differential, and cell viability. It is not necessary to look at internal organs. It is recommended that a recovery period of 60 days be included to assess the progression or regression of any lesions.

(e) Test Reports. The Company shall: (1) conduct each study in good faith, with due care, and in a scientifically valid manner; (2) promptly furnish to EPA the results of any interim phase of each study; and (3) submit the final report of each study (with an additional sanitized copy, if confidential business information is involved) and all underlying data ("the report and data") to EPA prior to exceeding the applicable production limit. The final report and data must be submitted as a support document for the PMN, using the procedures set out in 40 CFR 720.40. The final report shall contain the contents specified in 40 CFR 792.185. Underlying data shall be submitted to EPA in accordance with the applicable "Reporting," "Data and Reporting," and "Test Report" subparagraphs in the applicable test guidelines. However, for purposes of this Consent Order, the word "should" in those subparagraphs shall be interpreted to mean "shall" to make clear that the submission of such information is mandatory. EPA will require the submission of raw data such as slides and laboratory notebooks only if EPA finds, on the basis of professional judgment, that an adequate evaluation of the study cannot take place in the absence of these items.

(f) Testing Waivers. The Company is not required to conduct a study specified in paragraph (d) of this Testing section if notified in writing by EPA that it is unnecessary to conduct that study.

(g) Equivocal Data. If EPA finds that the data generated by a study are scientifically equivocal, the Company may continue to manufacture (which includes import) the PMN substance beyond the applicable production limit. To seek relief from any other restrictions of this Order, the Company may make a second attempt to obtain unequivocal data by reconducting the study under the conditions specified in paragraphs (b), (c), and (e) (except that the study may be submitted after reaching the applicable production limit). The testing requirements may be modified, as necessary to permit a reasoned evaluation of the risks presented by the PMN substance, only by mutual consent of EPA and the Company.

(h) EPA Determination of Invalid Data.

(1) Except as described in subparagraph (h)(2), if, within 6 weeks of EPA's receipt of a test report and data, the Company receives written notice that EPA finds that the data generated by a study are scientifically invalid, the Company is prohibited from further manufacture (which includes import) of the PMN substance beyond the applicable production limit.

(2) The Company may continue to manufacture (which includes import) the PMN substance beyond the applicable production limit only if so notified, in writing, by EPA in response to the Company's compliance with either of the following subparagraphs (h)(2)(i) or (h)(2)(ii).

(i) If there is sufficient time to reconduct the study in compliance with paragraphs (b), (c), and (e) before exceeding the production limit specified in paragraph (d), the Company may reconduct the study. If there is insufficient time to reconduct the study in compliance with paragraphs (b), (c), and (e) before exceeding the production limit specified in paragraph (d), the Company may exceed the production limit, but must otherwise comply with paragraphs (b), (c),

and (e), and shall submit the report and data to EPA within a reasonable period of time, all as specified by EPA in the notice described in subparagraph (h)(1). EPA will respond to the Company, in writing, within 6 weeks of receiving the Company's report and data.

(ii) The Company may, within 4 weeks of receiving from EPA the notice described in subparagraph (h)(1), submit to EPA a written report refuting EPA's finding. EPA will respond to the Company, in writing, within 4 weeks of receiving the Company's report.

(i) Company Determination of Invalid Data.

(1) Except as described in subparagraph (i)(2), if the Company becomes aware that circumstances clearly beyond the control of the Company or laboratory will prevent, or have prevented, development of scientifically valid data under the conditions specified in paragraphs (c) and (e), the Company remains prohibited from further manufacture (which includes import) of the PMN substance beyond the applicable production limit.

(2) The Company may submit to EPA, within 2 weeks of first becoming aware of such circumstances, a written statement explaining why circumstances clearly beyond the control of the Company or laboratory will cause or have caused development of scientifically invalid data. EPA will notify the Company of its response, in writing, within 4 weeks of receiving the Company's report. EPA's written response may either:

(i) allow the Company to continue to manufacture (which includes import) the PMN substance beyond the applicable production limit, or

(ii) require the Company to continue to conduct, or to reconduct, the study in compliance with paragraphs (b), (c), and (e), if there is sufficient time to conduct or reconduct the study and submit the report and data to EPA before exceeding the production limit specified in

paragraph (d). If there is insufficient time for the Company to comply with paragraphs (b), (c), and (e) before exceeding the production limit specified in paragraph (d), the Company may exceed the production limit, but must otherwise comply with paragraphs (b), (c), and (e), and shall submit the report and data to EPA within a reasonable period of time, all as specified by EPA in the notice described in subparagraph (i)(2). EPA will respond to the Company, in writing, within 6 weeks of receiving the Company's report and data, as to whether the Company may continue to manufacture (which includes import) beyond the applicable production limit.

(j) Unreasonable Risk.

EPA may notify the Company in writing that EPA finds that the data generated by a study are scientifically valid and unequivocal and indicate that, despite the terms of this Order, the PMN substance will or may present an unreasonable risk of injury to human health or the environment. EPA's notice may specify that the Company undertake certain actions concerning further testing, manufacture (which includes import), processing, distribution, use and/or disposal of the PMN substance to mitigate exposures to or to better characterize the risks presented by the PMN substance. Within 2 weeks from receipt of such a notice, the Company must cease all manufacture (which includes import), processing, distribution, use and disposal of the PMN substance, unless either:

(1) within 2 weeks from receipt of the EPA notice, the Company complies with such requirements as the notice specifies; or

(2) within 4 weeks from receipt of the EPA notice, the Company submits to EPA a written report refuting EPA's finding and/or the appropriateness of any additional requirements imposed by EPA. The Company may continue to manufacture (which includes import), process,

distribute, use and dispose of the PMN substance in accordance with the terms of this Order pending EPA's response to the Company's written report. EPA will respond to the Company, in writing, within 4 weeks of receiving the Company's report. Within 2 weeks of receipt of EPA's written response, the Company shall comply with any requirements imposed by EPA's response or cease all manufacture (which includes import), processing, distribution, use and disposal of the PMN substance.

(k) Other Requirements. Regardless of the satisfaction of any other conditions in this Testing section, the Company must continue to obey all the terms of this Consent Order until otherwise notified in writing by EPA. The Company may, based upon submitted test data or other relevant information, petition EPA to modify or revoke provisions of this Consent Order pursuant to Part VI. of this Consent Order.

PROTECTION IN THE WORKPLACE

(a) Establishment of Program. During manufacturing, processing, and use of the PMN substance at any site controlled by the Company (including any associated packaging and storage and during any cleaning or maintenance of equipment associated with the PMN substance), the Company must establish a program whereby:

(1) Respiratory Protection. Each person who is reasonably likely to be exposed by inhalation in the work area to the PMN substance in the form listed in subparagraph (a)(2) of this section is provided with and is required to wear, at a minimum, a National Institute for Occupational Safety and Health ("NIOSH")-certified respirator with an Applied Protection Factor ("APF") of <2, from the respirators listed in subparagraph (a)(3) of this section, and the respirator

is used in accordance with OSHA and NIOSH respiratory protection requirements at 29 CFR 1910.134 and 42 CFR Part 84. All respirators must be issued, used, and maintained according to an appropriate respiratory protection program under the OSHA requirements in 29 CFR 1910.134.

(2) Physical States. The following physical states of airborne chemical substances are listed for subparagraphs (a)(1) of this section:

(i) Particulate (including solids or liquid droplets),

(ii) Gas/vapor (all substances in the gas form), or

(iii) Combination Gas/Vapor and Particulate (gas and liquid/solid physical states are both present; a good example is paint spray mist, which contains both liquid droplets and vapor).

(3) Authorized Respirators. The following NIOSH-certified respirators meet the minimum requirements for subparagraph (a)(1) of this section:

Assigned Protection Factor (APF)	Type of Respirator
10	(I)Any NIOSH-certified **air-purifying** elastomeric half-mask respirator equipped with N100 (if oil aerosols absent), R100, or P100 filters. (II) Any appropriate NIOSH-certified N100 (if oil aerosols absent), R100, or P100 **filtering facepiece** respirator. [Note: for filtering facepieces, an APF of 10 can only be achieved if the respirator is qualitatively or quantitatively fit tested on individual workers]. (III) Any NIOSH-certified **air-purifying** full facepiece respirator equipped with N100 (if oil aerosols absent), R100, or P100 filters. (IV) Any NIOSH-certified negative pressure (demand) **supplied-air** respirator equipped with a half-mask. (V) Any NIOSH-certified negative pressure (demand) **self-contained**

Assigned Protection Factor (APF)	Type of Respirator
	breathing apparatus (SCBA) equipped with a half mask.

***A full facepiece air-purifying respirator, although it has a higher APF of 50, is required to provide full face protection because the PMN substance presents significant exposure concern for mucous membranes, eyes, or skin.**

(b) De Minimis Concentrations. The requirements of this section do not apply to quantities of the PMN substance that are (1) present in the work area only as a mixture and (2) at a concentration not to exceed 1.0 percent by weight or volume (0.1 percent by weight or volume if the PMN substance is identified as a potential carcinogen in paragraph (f) of the Hazard Communication Program section of this Order). This exemption is not available if the Company has reason to believe that, during intended activities, the PMN substance in the mixture may be reconcentrated above the 1.0 or 0.1 percent level, whichever applies. If this Order contains New Chemical Exposure Limits provisions or Release to Water provisions that, respectively, specify a NCEL concentration ("TWA") or in-stream concentration ("N") less than the de minimis concentration specified here, then this de minimis exemption does not apply to those provisions.

RISK NOTIFICATION

(a) If as a result of the test data required under the terms of this Order, the Company becomes aware that the PMN substance may present a risk of injury to health (or is so notified by EPA), the Company must incorporate this new information, and any information on methods for protecting against such risk, into a Material Safety Data Sheet ("MSDS"), as described in 40 CFR section 721.72(c), within 90 days from the time the Company becomes aware of the new information. If

the PMN substance is not being manufactured (which includes import), processed, or used in the Company's workplace, the Company must add the new information to an MSDS before the PMN substance is reintroduced into the workplace.

(b) The Company must ensure that persons who will receive the PMN substance from the Company, or who have received the PMN substance from the Company within 5 years from the date the Company becomes aware of the new information described in paragraph (a) of this section, are provided an MSDS containing the information required under paragraph (a) within 90 days from the time the Company becomes aware of the new information.

NEW CHEMICAL EXPOSURE LIMIT

(a) Alternative to Requirements of Respirator Section.

(1) EPA recommends and encourages the use of pollution prevention, source reduction, engineering controls and work practices, rather than respirators, as a means of controlling inhalation exposures whenever practicable.

(2) Whenever a person is reasonably likely to be exposed to the PMN substance by inhalation, as an alternative to compliance with the respirator requirements in the Protection in the Workplace section of this Order, the Company may comply with the requirements of this New Chemical Exposure Limit section. However, before the Company may deviate from the respirator requirements in the Protection in the Workplace section of this Order, the Company must:

(i) submit to EPA a copy of the Company's sampling and analytical method for the PMN substance, verified in accordance with subsection (c)(3) of this New Chemical Exposure Limit section;

(ii) obtain exposure monitoring results in accordance with this New Chemical Exposure Limit section; and

(iii) based on those exposure monitoring results, select, provide, and ensure use if necessary of the appropriate respiratory protection specified in paragraph (e)(2) of this New Chemical Exposure Limit section by persons who are reasonably likely to be exposed to the PMN substance by inhalation.

(3) After appropriate respiratory protection has been selected at a workplace based on the results of actual exposure monitoring conducted in accordance with this New Chemical Exposure Limit section, the Company shall not, at that workplace, use the respiratory protection required in the Protection in the Workplace section of this Order (unless it is the same as required by this New Chemical Exposure Limit section).

(b) Exposure Limit.

(1) General. The following new chemical exposure limit ("NCEL") for the PMN substance is an interim level determined by EPA based on the limited information available to the Agency at the time of development of this Order. The NCEL for the PMN substance is as follows:

(i) Time-Weighted Average ("TWA") Limit. The Company shall ensure that no person is exposed to an airborne concentration of the PMN substance in excess of 2.4 mg/m^3 as a 8–hour time weighted average, without using a respirator in accordance with subsection (e) of this New Chemical Exposure Limit section.

(ii) Non-8-Hour Work-shifts. For non-8-hour work-shifts, the NCEL for that work-shift (NCELn) shall be determined by the following equation: NCELn = NCEL x (8/n) x [(24-n)/16], where n = the number of hours in the actual work-shift.

(2) Automatic Sunset. If, subsequent to the effective date of this Order, OSHA promulgates, pursuant to §6 of the Occupational Safety and Health Act, 29 U.S.C. 655, a final chemical-specific permissible exposure limit ("PEL") specifically applicable to this PMN substance and the OSHA PEL is not challenged in court within 60 days of its promulgation, then any respirator requirements in the Protection in the Workplace section of this Order and any requirements of this New Chemical Exposure Limit section applicable to workers and situations subject to the OSHA PEL shall automatically become null and void. However, the requirements of this Consent Order are not negated by any pre-existing OSHA PEL applicable to the PMN substance.

(c) Performance-Criteria for Sampling and Analytical Method.

(1) Applicability. For initial development and validation of the sampling and analytical method for the PMN substance, all the requirements of this subsection (c) apply. For subsequent exposure monitoring conducted pursuant to subsection (d) of this New Chemical Exposure Limit section, only the following requirements apply: (c)(4)(i), (4)(ii), (4)(iv)(B), (4)(v)(B), (8), (9), and (10). Any deviation from the requirements of this subsection (c) must be approved in writing by EPA.

(2) Submission of Verified Method and Certification Statement. The Company shall submit to EPA a copy of a validated sampling and analytical method for the PMN substance which satisfies the criteria specified in this subsection (c). The method description shall expressly state how the method compares with each quantitative requirement specified in this subsection (c). The submission must include a written statement, signed by authorized officials of both the Company and the Laboratory, certifying the truth and accuracy of the independent laboratory verification

conducted pursuant to subsection (c)(3). To assist EPA in identifying the document, it shall state in a conspicuous, underlined subject-line at the top of the first page: "NCEL Sampling and Analytical Method for PMN **#P-11-150**," after-which the correct PMN number for this chemical substance shall be stated.

(3) Verification of Analytical Method by Independent Third-Party Laboratory.

(i) Verification. The Company shall have an independent reference laboratory ("Laboratory") verify the validity of the analytical method for the PMN substance, in accordance with the other requirements in this subsection (c)(3). It is the Company's responsibility to ensure that the Laboratory complies with all the requirements specified in this subsection (c)(3).

(ii) Independent Reference Laboratory. The independent reference laboratory must be a separate and distinct person (as defined at 40 CFR 720.3(x)) from the Company and from any other person who may have developed the method for the Company.

(iii) Accreditation. The Laboratory must be accredited by a formally recognized government or private laboratory accreditation program for chemical testing and/or analysis.

(iv) Good Laboratory Practice Standards. The Laboratory verification of the analytical method for the PMN substance must comply with TSCA Good Laboratory Practice Standards ("GLPS") at 40 CFR Part 792. [Certain provisions of the TSCA GLPS applicable to toxicity testing in laboratory animals, such as 40 CFR 792.43 ("Test system care facilities"), 792.45 ("Test system supply facilities") and 792.90 ("Animal and other test system care"), are clearly inapplicable to the NCEL requirements.] However, compliance with TSCA GLPS is not required under this New Chemical Exposure Limit section where the analytical method is verified by a laboratory accredited by either: (A) the American Industrial Hygiene Association ("AIHA") Industrial Hygiene Laboratory Accreditation Program ("IHLAP"); or (B) another comparable

program approved in advance in writing by EPA.

(v) Analysis of Duplicate Samples. The Company shall collect six duplicate samples (a total of 12) at the TWA concentration. The samples shall be taken either from a controlled environment (e.g., a sealed chamber or "glove box") which closely resembles the actual workplace conditions or, for solids and liquids with very low vapor pressure, by injecting the PMN substance onto a sample collection device. The duplicate samples shall be collected on identical collection media, at the same time, and under the same conditions. One set of six samples shall immediately be analyzed by the Company, the other set of six samples shall be analyzed by the Laboratory using the method developed by or for the Company.

(vi) Sample Storage Study. If the results of the analysis of duplicate samples pursuant to paragraph (c)(3)(v) do not satisfy the requirements in paragraph (c)(3)(vii), the Company must perform a sample storage study as follows:

(I) Triplicate Samples. The Company shall collect six triplicate samples (a total of 18) at the TWA concentration. The samples shall be taken either from a controlled environment (e.g., a sealed chamber or "glove box") which closely resembles the actual workplace conditions or, for solids and liquids with very low vapor pressure, by injecting the PMN substance onto a sample collection device. The triplicate samples shall be collected on identical collection media, at the same time, and under the same conditions. One set of six samples shall immediately be analyzed by the Company.

(II) Analysis After Sample Storage. A sample storage evaluation shall be performed with the two remaining sets of six samples. One set of six samples shall be analyzed by the Laboratory using the method developed by or for the Company, and the other shall be analyzed by the Company on the same day as the Laboratory analyzes its six samples. Specialized storage

conditions for the samples including extraction conditions, time from sampling to extraction, time from collection or extraction (if applicable) to analysis and storage conditions must be specified in the method description.

(vii) Comparison of Results. The difference between the results of the two sets of six samples analyzed by the Laboratory and the Company as required in either paragraph (c)(3)(v) or (c)(3)(vi)(II) shall be evaluated using a two-sample t-test with unequal variances, and the two sides of the critical regions shall not exceed a 5% significance level. (See Attachment B - Statistical Analysis of NCELs Analytical Method Verification Results.) The arithmetic mean of each set of six samples must be within 10% of the overall arithmetic mean of the two sets of sample measurements. If the arithmetic mean of each set of six samples is not within 10% of the overall arithmetic mean, then the sample storage time between collection and analysis must be reduced until the average of each set of six samples is within 10% of the overall arithmetic mean.

(4) Accuracy. The sampling and analytical method must clearly demonstrate the following:

(i) General. The sampling and analytical method, and all exposure monitoring data relied on by the Company, shall be accurate to within $\pm$25% at a 95% confidence level for concentrations of the PMN substance ranging from one half the NCEL to twice the NCEL.

(ii) NCEL Quantitation Limits. The analytical method should be capable of reliably quantifying the PMN substance across the full range of reasonably likely exposures. At a minimum, the analytical method must be capable of reliably quantifying from a lower quantitation limit ("LQL") of one half the NCEL to an upper quantitation limit ("UQL") of at least twice the NCEL. If the Company obtains an exposure monitoring sample that is more than 10% above the actual UQL of the analytical method, the Company must comply with paragraph (e)(4)(i).

(iii) Lower Quantitation Limit Signal-To-Noise Ratio. The analytical method shall be capable of quantifying the PMN to a concentration of one half the NCEL with a signal that is at least five times the baseline noise level. Baseline noise must be amplified to a measurable level when possible, even if the required amplification is beyond that used in routine analysis of samples. (If baseline noise cannot be obtained, another reference must be selected. This may be a peak considered to be noise caused by the reagent matrix.) The sampling preparation method must be specified and the detection limit for the analytical procedure must be reported as mass per injection for chromatographic techniques.

(iv) Instrument Calibration.

(I) Initial Calibration. For method development and validation (but not subsequent exposure monitoring), the initial calibration shall at a minimum consist of five (5) calibration standards with a linear correlation of 0.95 -- these five (5) calibration standards must consist of one standard at each of the following concentrations: one half the NCEL (0.5 x NCEL); between one half and one times the NCEL (0.5 x NCEL <> 1 x NCEL); one times the NCEL (1 x NCEL); between one and two times the NCEL (1 x NCEL <> 2 x NCEL), and twice the NCEL (2 x NCEL).

(II) Continuing Calibration. During each week of both method development/validation and subsequent exposure monitoring, the Company shall conduct both an initial instrument calibration and a continuing calibration. The Company shall perform at least one continuing calibration sample at the NCEL concentration, and at least one additional calibration sample per every 10 samples analyzed. The continuing calibration sample shall fall within $\pm$ 25% of the initial calibration value. If not, then the initial calibration must be repeated, and any samples associated with that outlying calibration check must be re-analyzed.

(v) Calculated Percent Recovery.

(I) Initial Calculation. For method development and validation, the Company must calculate the percent of the PMN substance recovered by the analytical method from a sample containing a known quantity of the PMN substance. The sample shall be taken either from a controlled environment (e.g., a sealed chamber or "glove box") which closely resembles the actual workplace conditions or, for solids and liquids with very low vapor pressure, by injecting the PMN substance onto a sample collection device. (Such a sample is referred to as a "matrix spike"). The calculated percent recovery for each matrix spike shall be greater than or equal to 75% and less than or equal to 125%. Spike concentrations for the PMN substance must be included in the sampling and analytical method submitted to EPA.

(II) Subsequent Calculation. During each subsequent exposure monitoring episode or campaign, at least 1 matrix spike, prepared by injecting the PMN substance onto a sample collection device, shall be analyzed. (This matrix spike must be prepared at the NCEL concentration.)

(vi) Sampling Device Capacity. The capacity of the sampling device must be tested and results reported to show under a known and well-defined set of conditions that the device is capable of collecting the new chemical in solid, liquid or vapor phase with minimal loss. The sampling device's capacity (air volume and collected analyte mass) must be specified. For methods that use adsorbent tubes as the collection medium, evidence of the capacity must be provided in the form of breakthrough testing. This testing must be done at a concentration twice the NCEL and under conditions similar to those expected in the workplace. Breakthrough is defined to have occurred when the concentration of the PMN substance in the effluent stream is equal to 5% of the concentration of the influent stream, or when 20% of the PMN substance is

detected in the backup section of the sampler.

(vii) Sampling Device Desorption Efficiency. Where applicable, the desorption efficiency must be evaluated for the air sampling device. A minimum of six air samples spiked with the PMN substance at least the NCEL concentration must be prepared. A recovery of at least 75% must be obtained for each of the six samples.

(5) Precision. The estimate of the coefficient of variation of each set of six samples from the controlled atmosphere test (spiked at 1.0 NCEL, per paragraphs (c)(3)(v) or (vi)) must be less than 0.105, including allowance of 0.05 for error due to sampling.

(6) Interpretation of Accuracy and Precision Data.

(i) If a single matrix spike recovery is less than 75% recovery or greater than 125% or the estimated precision is greater than 0.105, then the Company must re-prepare the matrix spike, re-sample, and re-analyze all samples associated with such matrix spike or triplicate samples.

(ii) For percent recoveries less than 90% but greater than 75%, correction for low recovery is required. Correct for recovery first by dividing the observed amount by the proportion recovered before determining if measurements fall below the NCEL. For example, if the observed level is 30 mg/m^3 and the percent recovery is 75%, use the value 30 $mg/m^3/(0.75) = 40$ mg/m^3 when determining whether the levels are below the exposure limit.

(7) Representativeness. All sample conditions used to develop the methodology shall mimic the actual workplace environment expected to be monitored. Conditions such as the temperature, humidity, lighting, and presence of other chemicals, etc. must mimic the conditions in the workplace to be monitored.

(8) Changes Affecting Validity. If the workplace environment changes from the initial

conditions described in the verified sampling and analytical method in a way reasonably likely to invalidate the accuracy of the method, then the Company must comply with the respirator requirements in the Protection in the Workplace section of this Order, unless the Company re-validates the method to confirm that the requirements for accuracy and precision in paragraphs (c)(4) and (5) are met. Examples of possible changes include but are not limited to: introduction of a new chemical substance to the workplace which may interfere with the analysis of the new chemical; introduction of light to the workplace which may interfere with a light-sensitive PMN substance; or introduction of water/increased humidity to the workplace which could react with the PMN substance and cause difficulties in collection and analysis.

(9) Comparability. All data and results shall be reported in the same units of measurement as the NCEL.

(10) Responsibility for Method Validity. The independent laboratory verification and EPA receipt of the sampling and analytical method pursuant to this subsection (c) do not ensure that the method will produce valid exposure monitoring data. The Company is ultimately responsible for ensuring the validity of its exposure monitoring data.

(d) Monitoring Potential Exposure.

(1) General.

(i) Action Level. The "action level" is defined as an airborne concentration of the PMN substance, calculated as an 8-hour time-weighted average, equal to one half the NCEL TWA specified in subparagraph (b)(1). For non-8-hour work shifts, the action level is equal to one half the NCELn. (The NCELn is described in subparagraph (b)(1)(ii).) The Company may exceed the action level without penalty. The purpose of the action level is solely to determine the requisite

monitoring frequency.

(ii) Representative Exposure Groups. Whenever exposure monitoring is required by this New Chemical Exposure Limit section, the Company shall take representative samples of what the potential exposure of each person who is reasonably likely to be exposed to airborne concentrations of the PMN substance would be if respirators were not worn. The Company shall do so by sampling the breathing zone air of at least one person that represents, and does not underestimate, the potential exposure of every person performing the same or substantially similar operations in each work shift, in each job classification, in each work area (hereinafter identified as an "exposure group") where inhalation exposure to the PMN substance is reasonably likely to occur. The exposure of each person need not be itself directly sampled if that exposure is represented by sampling the exposure of another person in the same exposure group.

(iii) Good Laboratory Practice Standards. Determinations of potential inhalation exposure shall be made according to TSCA Good Laboratory Practice Standards at 40 CFR Part 792 and the sampling and analytical method developed pursuant to subsection (c) of this New Chemical Exposure Limit section. [Certain provisions of the TSCA GLPS applicable to toxicity testing in laboratory animals, such as 40 CFR 792.43 ("Test system care facilities"), 792.45 ("Test system supply facilities") and 792.90 ("Animal and other test system care"), are clearly inapplicable to the NCEL requirements.] However, compliance with TSCA GLPS is not required where exposure monitoring samples are analyzed by a laboratory accredited by either: (A) the American Industrial Hygiene Association ("AIHA") Industrial Hygiene Laboratory Accreditation Program ("IHLAP"); or (B) another comparable program approved in advance in writing by EPA.

(iv) Full Shift Exposure Samples. Representative 8-hour TWA airborne concentrations shall be determined on the basis of samples representing the full shift exposure for

each exposure group.

2) Initial Monitoring. Before the Company may deviate from the respirator requirements of the Protection in the Workplace section, the Company shall conduct initial exposure monitoring to accurately determine the airborne concentration of the PMN substance for each exposure group in which persons are reasonably likely to be exposed to the PMN substance.

(3) Periodic Monitoring.

(i) If any representative samples taken during the initial exposure monitoring reveal an airborne concentration at or above the action level but at or below the TWA, the Company shall repeat the exposure monitoring for that exposure group at least every 6 months. If the PMN substance is not manufactured (which includes import), processed, or used at all during a given 6 month calendar period, the Company is not required to conduct exposure monitoring until manufacture (which includesimport), processing, or use of the PMN substance is resumed. However, cessation of manufacturing, processing and use of the PMN substance for less than the 6 month period does not constitute grounds for postponement of the 6 month deadline to conduct exposure monitoring.

(ii) If any representative samples taken during the initial exposure monitoring reveal an airborne concentration above the TWA, the Company shall repeat the exposure monitoring for that exposure group at least every 3 months. If the PMN substance is not manufactured (which includes import), processed, or used at all during a given 3 month calendar period, the Company is not required to conduct exposure monitoring until manufacture (which includes import), processing, or use of the PMN substance is resumed. However, cessation of manufacturing (including import), processing and use of the PMN substance for less than the 3 month period does not constitute grounds for postponement of the 3 month deadline to conduct

exposure monitoring.

(iii) The Company may alter the exposure monitoring schedule from every 3 months to every 6 months for any exposure group for whom two consecutive measurements taken at least 7 days apart indicate that the potential exposure has decreased to the TWA or below, but is at or above the action level. Where the PMN substance is manufactured (which includes import), processed, or used in batches of duration less than 7 days, the 2 consecutive measurements may be taken at least 24 hours apart, provided that the measurements accurately reflect the highest peak exposures and variability in exposure.

(4) Termination of Monitoring.

(i) If representative samples taken during the initial exposure monitoring reveal an airborne concentration below the action level, the Company may discontinue monitoring for that exposure group, except when additional exposure monitoring is required by paragraph (d)(5) of this New Chemical Exposure Limit section.

(ii) If representative samples taken during the periodic monitoring reveal that an airborne concentration, as indicated by at least 2 consecutive measurements taken at least 7 days apart, are below the action level, the Company may discontinue the monitoring for that exposure group, except when additional monitoring is required by paragraph (d)(5) of this New Chemical Exposure Limit section. Where the PMN substance is manufactured (which includes import), processed, or used in batches of duration less than 7 days, the 2 consecutive measurements may be taken at least 24 hours apart, provided that the measurements accurately reflect the highest peak exposures and variability in exposure.

(5) Additional Monitoring.

(i) For a previously monitored exposure group, the Company shall, within 7 days

of any of the events listed below in this paragraph (d)(5)(i), conduct the initial exposure monitoring followed by any periodic or additional exposure monitoring required by subsection (d) of this New Chemical Exposure Limit section:

(I) change in the production volume, process, control equipment, personnel or work practices that may reasonably cause new or additional exposures to the PMN substance;

(II) spills, leaks, ruptures or other breakdowns occur that may reasonably cause new or additional exposures to the PMN substance; and,

(III) whenever else the Company has any reason to suspect a change that may reasonably result in new or additional exposures to the PMN substance.

(ii) In no event is the additional exposure monitoring requirement in paragraph (d)(5)(i) intended to delay implementation of any necessary cleanup or other remedial action. During any cleanup or remedial operations that may occur before commencing additional exposure monitoring, the Company shall ensure that potentially exposed persons use at least the respiratory protection specified in subsection (e) for the measured airborne concentration, or more protective respiratory equipment deemed appropriate by the best professional judgment of a qualified expert.

(6) Notification of Monitoring Results.

(i) Within 15 working days after receipt of the results of any exposure monitoring required by this Order, the Company shall notify each person whose exposure is represented by that monitoring. The notice shall identify the NCEL, the exposure monitoring results, and any corresponding respiratory protection required by subsection (e). Affected persons shall be notified in writing either individually or by posting the information in an appropriate and accessible location:

(ii) Whenever the NCEL is exceeded, the written notification required by the

preceding paragraph shall describe the action being taken by the Company to reduce inhalation exposure to or below the NCEL, or shall refer to a document available to the person which states the actions to be taken to reduce exposure.

(7) Exemption based on Objective Data. Where the Company has documented and reliable objective data demonstrating that, even under worst-case conditions, employee exposure to the PMN substance will not exceed the action level (defined in paragraph (d)(1)(i)) under the expected handling procedures and conditions for a specific "exposure group" (defined in paragraph (d)(1)(ii)), then that exposure group is exempt from this New Chemical Exposure Limit section (except paragraph (d)(5) "Additional Monitoring" and subsection (f) "NCEL Record-keeping") and the respirator requirements in the Protection in the Workplace section of this Order. Any such objective data must accurately characterize actual employee exposures to the PMN substance and must be obtained under conditions closely resembling the types of materials, processes, control methods, work practices, and environmental conditions in the Company's current workplace operations with the PMN substance. Examples of objective data that may be used to demonstrate that employee exposure will not exceed the action level, even under worst case conditions, include information on the physical and chemical properties of the PMN substance, industry-wide studies, and/or laboratory test results.

(e) Respiratory Protection.

(1) General. Whenever the Company has conducted exposure monitoring at a workplace in accordance with subsection (d) of this New Chemical Exposure Limit section and the measured airborne concentration of the PMN substance for any person who is reasonably likely to be exposed to the PMN substance by inhalation exceeds the NCEL, the Company shall provide those

persons the respirators specified in this subsection (e) (rather than the respirator(s) identified in the Protection in the Workplace section of this Order), and shall ensure that the respirators are used (including training, fit testing, and maintenance) in accordance with OSHA and NIOSH respiratory protection requirements at 29 CFR 1910.134 and 42 CFR Part 84. When the Company has not yet measured the airborne concentration of the PMN substance at a workplace in accordance with this New Chemical Exposure Limit section, the Company shall comply with the respirator requirements in the Protection in the Workplace section of this Order at that workplace.

(2) Selection of Appropriate Respiratory Protection. After the Company has conducted exposure monitoring in accordance with subsection (d) of this New Chemical Exposure Limit section, the Company shall select, provide, and ensure that persons who are reasonably likely to be exposed to the PMN substance by inhalation use, at a minimum, the respiratory protection which corresponds in the following table to the measured airborne concentration (or a more protective respirator which corresponds to a concentration higher than measured).

PARTICULATE RESPIRATOR TABLE

Measured Concentration of PMN Substance	**Required Respiratory Protection**
≤ NCEL	No respiratory protection is required.
≤ 10 x NCEL	I) Any NIOSH-certified **air-purifying** elastomeric half-mask respirator equipped with N100 (if oil aerosols absent), R100, or P100 filters (II) Any appropriate NIOSH-certified N100 (if oil aerosols absent), R100, or P100 **filtering facepiece** respirator. [Note: for filtering facepieces, an APF of 10 can only be achieved if the respirator is qualitatively or quantitatively fit tested on individual workers

(III) Any NIOSH-certified **air-purifying** full facepiece respirator equipped with N100 (if oil aerosols absent), R100, or P100 filters. (IV) Any NIOSH-certified negative pressure (demand) **supplied-air** respirator equipped with a half-mask.

(V) Any NIOSH-certified negative pressure (demand) **self-contained breathing apparatus** (SCBA) equipped with a half mask

***A full facepiece air-purifying respirator, although it has a higher APF of 50, is required to provide full face protection because the PMN substance presents significant exposure concern for mucous membranes, eyes, or skin.**

≤ 25 x NCEL

(I) Any NIOSH-certified **powered air-purifying** respirator equipped with a hood or helmet and HEPA filters.

(II) Any NIOSH-certified **powered air-purifying** respirator equipped with a loose fitting facepiece and HEPA filters.

(III) Any NIOSH-certified continuous flow **supplied-air** respirator equipped with a hood or helmet.

(IV) Any NIOSH-certified continuous flow **supplied-air** respirator equipped with a loose fitting facepiece.

≤ 50 x NCEL

(I) Any NIOSH-certified **air-purifying** full facepiece respirator equipped with N100 (if oil aerosols absent), R-100, or P-100 filter(s).

(II) Any NIOSH-certified **powered air-purifying** respirator equipped with a tight-fitting facepiece (half or full facepiece) and equipped with HEPA filters. (III) Any NIOSH-certified pressure-demand or other positive pressure mode **supplied-air** respirator equipped with a half-mask. (IV) Any NIOSH-certified negative pressure (demand) **supplied-air** respirator equipped with a full facepiece.

(V) Any NIOSH-certified continuous flow **supplied-air** respirator equipped with a tight-fitting facepiece (half or full facepiece)

(VI) Any NIOSH-certified negative pressure (demand) **self-contained breathing apparatus** (SCBA) equipped with a hood or helmet or a full facepiece..

≤ 1000 x NCEL

(I) Any NIOSH-certified **powered air purifying** full facepiece respirator equipped with HEPA filters.

(II) Any NIOSH-certified **powered air-purifying** respirator equipped with a hood or helmet* and N100 (if oil aerosols absent), R100, or P100 filters *with evidence demonstrating protection level of 1,000 or greater.** (III) Any NIOSH-certified continuous flow **supplied-air** respirator equipped with a full facepiece.

(IV) Any NIOSH-certified continuous flow **supplied-air** respirator equipped with a hood or helmet *with evidence demonstrating protection level of 1,000 or greater.* *

(V) Any NIOSH-certified **supplied-air** respirator equipped with a full facepiece.

* OSHA has assigned APFs of 1000 for certain types of hoods and helmets with powered air purifying respirators (PAPRs) or supplied air respirators (SARs) where the manufacturer can demonstrate adequate air flows to maintain positive pressure inside the hood or helmet in normal working conditions. However, the employer must have evidence provided by the respirator manufacturer that the testing of these respirators demonstrates performance at a level of protection of 1,000 or greater to receive an APF of 1,000. This level of performance can best be demonstrated by performing a Workplace Protection Factor (WPF) or Simulated Workplace Protection Factor (SWPF) study or equivalent testing. **Without testing data that demonstrates a level of protection of 1,000 or greater, all PAPRs and SARs with helmets/hoods are to be treated as loose-fitting facepiece respirators, and receive an APF of 25.**

> 1000 x NCEL (max. 10,000 x NCEL)	Any NIOSH-certified pressure-demand or other positive pressure mode (e.g., open/closed circuit) **self-contained breathing apparatus** (SCBA) equipped with a hood or helmet or a full facepiece.

(3) Reductions in Respiratory Protection. After appropriate respiratory protection has been selected based on the results of actual exposure monitoring conducted at a workplace in accordance with subsection (d) of this New Chemical Exposure Limit section, the Company shall not, at that workplace, use the respiratory protection required by the Protection in the Workplace section of this Order (unless it is the same as required by this New Chemical Exposure Limit section). Before the Company may make any reduction in any respiratory protection selected pursuant to this New Chemical Exposure Limit section, the Company must verify, by 2 consecutive measurements taken at least 7 days apart, that the new respiratory protection is appropriate in accordance with paragraph (e)(2). Where the PMN substance is manufactured

(which includes import), processed, or used in batches of duration less than 7 days, the 2 consecutive measurements may be taken at least 24 hours apart, provided that the measurements accurately reflect the highest peak exposures and variability in exposure.

(4) Special Situations.

(i) Measurements Outside Quantitation Limits. When a value less than the lower quantitation limit ("LQL") of the analytical method (as described in paragraph (c)(4)(ii)) is measured, the Company shall estimate potential exposure using generally established and accepted statistical methods. If the Company obtains an exposure monitoring sample that is more than 10% above the actual upper quantitation limit ("UQL") of the analytical method, the Company must ensure that its workers wear at least a NIOSH-certified supplied-air respirator operated in pressure demand or other positive pressure mode and equipped with a tight-fitting full facepiece. Any reductions in this respiratory protection must comply with paragraph (e)(3). The Company may submit an improved analytical method provided that it complies fully with subsection (c) of this New Chemical Exposure Limit section, including the verification required by subsection (c)(3).

(ii) Cleanup and Remedial Actions. During any special cleanup or other remedial actions that may occur before commencing additional exposure monitoring (as discussed in paragraph (d)(5)(ii)), the Company shall ensure that potentially exposed persons use at least the respiratory protection specified above in this subsection (e) for the measured airborne concentration, or more protective respiratory equipment deemed appropriate by the best professional judgment of a qualified expert.

(f) NCEL Recordkeeping.

(1) Whenever the Company elects to comply with this New Chemical Exposure Limit

section rather than the respirator requirements in the Protection in the Workplace section of this Order, the Company shall maintain the following records until 30 years after the date they are created, and shall make them available for inspection and copying by EPA in accordance with section 11 of TSCA:

(i) A copy of the sampling and analytical methods used and continuing evidence of their accuracy over time as required by section (c);

(ii) Records documenting compliance with the analytical method verification requirements of subsection (c)(3), including copies of the signed certification statement and the verification results obtained by both laboratories;

(iii) Records documenting either compliance with the Good Laboratory Practice Standards at 40 CFR Part 792, or use of a laboratory accredited by the American Industrial Hygiene Association ("AIHA") or another comparable program approved in advance in writing by EPA. Where the Company elects to not comply with TSCA GLPS, such records shall include the written accreditation from the AIHA or the written approval from EPA.

(iv) Records documenting all exposure monitoring dates, duration, and results of each sample taken;

(v) Records documenting the name, address, work shift, job classification, and work area of the person monitored and of all other persons whose exposures the monitoring is intended to represent;

(vi) Any conditions that might have affected the monitoring results;

(vii) Notification of exposure monitoring results required by paragraph (d)(6);

(viii) Records documenting any changes in the production, process, control equipment, personnel or work practices that may reasonably cause new or additional exposures to

the PMN substance;

(ix) Records documenting any spills, leaks, ruptures or other breakdowns that may cause new or additional exposure;

(x) The type of respiratory protective devices worn by the monitored person, if any;

(xi) Records documenting any actions taken to mitigate exposures to the PMN substance;

(xii) Records documenting reliance on the objective data exemption in paragraph (d)(7), including: (A) the source of the data, (B) protocols and results of any relevant testing or analysis, (C) a description of the operation exempted and how the data demonstrate that employee exposures will not exceed the action level, (D) other data relevant to the operations, materials and employee exposures covered by the exemption.

HAZARD COMMUNICATION PROGRAM

(a) Written Hazard Communication Program. The Company shall develop and implement a written hazard communication program for the PMN substance in each workplace. The written program will, at a minimum, describe how the requirements of this section for labels, MSDSs, and other forms of warning material will be satisfied. The Company must make the written hazard communication program available, upon request, to all employees, contractor employees, and their designated representatives. The Company may rely on an existing hazard communication program, including an existing program established under the OSHA Hazard Communication Standard (29 CFR 1910.1200), to comply with this paragraph provided that the existing hazard communication program satisfies the requirements of this section. The written program shall include the following:

(1) A list of chemical substances known to be present in the work area which are subject to a TSCA section 5(e) consent order signed by the Company or to a TSCA section 5(a)(2) SNUR at 40 CFR Part 721, subpart E. The list must be maintained in each work area where the PMN substance is known to be present and must use the identity provided on the MSDS for the substance required under paragraph (c) of this section. The list may be compiled for the workplace or for individual work areas. If the Company is required either by another Order issued under section 5(e) of TSCA, or by a TSCA section 5(a)(2) SNUR at 40 CFR Part 721, subpart E, to maintain a list of substances, the lists shall be combined with the list under this subparagraph.

(2) The methods the Company will use to inform employees of the hazards of non-routine tasks involving the PMN substance (e.g., cleaning of reactor vessels), and the hazards associated with the PMN substance contained in unlabeled pipes in their work area.

(3) The methods the Company will use to inform contractors of the presence of the PMN substance in the Company's workplace and of the provisions of this Order if employees of the contractor work in the Company's workplace and are reasonably likely to be exposed to the PMN substance while in the Company's workplace.

(b) Labeling.

(1) The Company shall ensure that each container of the substance in the workplace is labeled in accordance with this subparagraph (b)(1).

(i) The label shall, at a minimum, contain the following information:

(A) A statement of the health hazards(s) and precautionary measure(s), if any, identified either in paragraph (f) of this section or by the Company, for the PMN substance.

(B) The identity by which the PMN substance may be commonly recognized.

(C) A statement of the environmental hazard(s) and precautionary measure(s), if any, identified either in paragraph (f) of this section, or by the Company, for the PMN substance.

(D) A statement of exposure and precautionary measure(s), if any, identified either in paragraph (f) of this section, or by the Company, for the PMN substance.

(ii) The Company may use signs, placards, process sheets, batch tickets, operating procedures, or other such written materials in lieu of affixing labels to individual stationary process containers, as long as the alternative method identifies the containers to which it is applicable and conveys information specified by subparagraph (b)(1)(i) of this section. Any written materials must be readily accessible to the employees in their work areas throughout each work shift.

(iii) The Company need not label portable containers into which the PMN substance is transferred from labeled containers, and which are intended only for the immediate use of the employee who performs the transfer.

(iv) The Company shall not remove or deface an existing label on containers of the PMN substance obtained from persons outside the Company unless the container is immediately re-labeled with the information specified in subparagraph (b)(1)(i) of this section.

(2) The Company shall ensure that each container of the substance leaving its workplace for distribution in commerce is labeled in accordance with this subparagraph (b)(2).

(i) The label shall, at a minimum, contain the following information:

(A) The information prescribed in subparagraph (b)(1)(i) of this section.

(B) The name and address of the manufacturer or a responsible party who can provide additional information on the substance for hazard evaluation and any appropriate emergency procedures.

(ii) The label shall not conflict with the requirements of the Hazardous Materials Transportation Act (18 U.S.C. 1801 et. seq.) and regulations issued under that Act by the Department of Transportation.

(3) The label, or alternative forms of warning, shall be legible and prominently displayed.

(4) The label, or alternative forms of warning, shall be printed in English; however, the information may be repeated in other languages.

(5) If the label or alternative form of warning is to be applied to a mixture containing the PMN substance in combination with any other substance that is either subject to another TSCA section 5(e) Order applicable to the Company, or subject to a TSCA section 5(a)(2) SNUR at 40 CFR Part 721, subpart E, or defined as a "hazardous chemical" under the OSHA Hazard Communication Standard (29 CFR 1900.1200), the Company may prescribe on the label, MSDS, or alternative form of warning, the measures to control worker exposure or environmental release which the Company determines provide the greatest degree of protection. However, should these control measures differ from the applicable measures required under this Order, the Company must seek a determination of equivalency for such alternative control measures pursuant to 40 CFR 721.30 before prescribing them under this subparagraph (b)(5).

(6) If the Company becomes aware of any significant new information regarding the hazards of the PMN substance or ways to protect against the hazards, this new information must be added to the label within 3 months from the time the Company becomes aware of the new information. If the PMN substance is not being manufactured (which includes import), processed,

or used in the Company's workplace, the Company must add the new information to the label before the PMN substance is reintroduced into the workplace.

(c) Material Safety Data Sheets.

(1) The Company must obtain or develop an MSDS for the PMN substance.

(2) The MSDS shall contain, at a minimum, the following information:

(i) The identity used on the container label of the PMN substance under this section, and, if not claimed confidential, the chemical and common name of the PMN substance. If the chemical and common names are claimed confidential, a generic chemical name must be used.

(ii) Physical and chemical characteristics of the substance known to the Company, (e.g., vapor pressure, flash point).

(iii) The physical hazards of the substance known to the Company, including the potential for fire, explosion, and reactivity.

(iv) The potential human and environmental hazards as specified in paragraph (f) of this section.

(v) Signs and symptoms of exposure, and any medical conditions which are expected to be aggravated by exposure to the PMN substance known to the Company.

(vi) The primary routes of exposure to the PMN substance.

(vii) Precautionary measures to control worker exposure and/or environmental release required by this Order, or alternative control measures which EPA has determined under 40 CFR 721.30 provide substantially the same degree of protection as the identified control measures. The MSDS must identify any New Chemical Exposure Limits specified in paragraph (b) of the

New Chemical Exposure Limit section of this Order and must contain the information specified in the graduated respirator table in paragraph (e)(2) of the New Chemical Exposure Limit section.

(viii) Any generally applicable precautions for safe handling and use of the PMN substance which are known to the Company, including appropriate hygienic practices, protective measures during repair and maintenance of contaminated equipment, and procedures for response to spills and leaks.

(ix) Any generally applicable control measures which are known to the Company, such as appropriate engineering controls, work practices, or personal protective equipment.

(x) Emergency first aid procedures known to the Company.

(xi) The date of preparation of the MSDS or of its last revision.

(xii) The name, address, and telephone number of the Company or another responsible party who can provide additional information on the chemical substance and any appropriate emergency procedures.

(3) If no relevant information is found or known for any given category on the MSDS, the Company (or parent Company) must mark the MSDS to indicate that no applicable information was found.

(4) Where multiple mixtures containing the PMN substance have similar compositions (i.e., the chemical ingredients are essentially the same, but the specific composition varies from mixture to mixture) and similar hazards, the Company may prepare one MSDS to apply to all of these multiple mixtures.

(5) If the Company becomes aware of any significant new information regarding the hazards of the PMN substance or ways to protect against the hazards, this new information must be added to the MSDS within 3 months from the time the Company becomes aware of the new

information. If the PMN substance is not being manufactured (which includes import), processed, or used in the Company's workplace, the Company must add the new information to the MSDS before the PMN substance is reintroduced into the workplace.

(6) The Company must ensure that persons receiving the PMN substance from the Company are provided an appropriate MSDS with their initial shipment and with the first shipment after an MSDS is revised. The Company may either provide the MSDS with the shipped containers or send it to the person prior to or at the time of shipment.

(7) The Company must maintain a copy of the MSDS in its workplace, and must ensure that it is readily accessible during each work shift to employees when they are in their work areas.

(8) The MSDS may be kept in any form, including as operating procedures, and may be designed to cover groups of substances in a work area where it may be more appropriate to address the potential hazards of a process rather than individual substances. However, in all cases, the required information must be provided for the PMN substance and must be readily accessible during each work shift to employees when they are in their work areas.

(9) The MSDS must be printed in English; however, the information may be repeated in other languages.

(d) Employee Information and Training. The Company must ensure that employees are provided with information and training on the PMN substance. This information and training must be provided at the time of each employee's initial assignment to a work area containing the PMN substance and whenever the PMN substance is introduced into the employee's work area for the first time.

(1) The information provided to employees under this paragraph shall include:

(i) The requirements of this section.

(ii) Any operations in the work area where the PMN substance is present.

(iii) The location and availability of the written hazard communication program required under paragraph (a) of this section, including the list of substances required by subparagraph (a)(1) of this section and MSDSs required by paragraph (c) of this section.

(2) The training provided to employees shall include:

(i) Methods and observations that may be used to detect the presence or release of the PMN substance in or from an employee's work area (such as exposure monitoring conducted by the Company, continuous monitoring devices, visual appearance, or odor of the substance when being released).

(ii) The potential human health hazards of the PMN substance as specified in paragraph (f) of this section.

(iii) The measures employees can take to protect themselves from the PMN substance, including specific procedures the Company has implemented to protect employees from exposure to the PMN substance, including appropriate work practices, emergency procedures, personal protective equipment, engineering controls, and other measures to control worker exposure required under this Order, or alternative control measures which EPA has determined under 40 CFR 721.30 provide the same degree of protection as the specified control measures.

(iv) The requirements of the hazard communication program developed by the Company under this section, including an explanation of the labeling system and the MSDS required by this section and guidance on obtaining and using appropriate hazard information.

(e) De Minimis Concentrations. The requirements of this Hazard Communication section do not apply to quantities of the PMN substance that are (1) present in the work area only as a mixture and (2) at a concentration not to exceed 1.0 percent by weight or volume (0.1 percent by weight or volume if the PMN substance is identified as a potential carcinogen in paragraph (f) of the Hazard Communication Program section of this Order). This exemption is not available if the Company has reason to believe that, during intended activities, the PMN substance in the mixture may be reconcentrated above the 1.0 or 0.1 percent level, whichever applies. If this Order contains (1) New Chemical Exposure Limits provisions that specify a NCEL concentration less than the de minimis concentration specified here, or (2) Release to Water provisions that prohibit release to water or specify in-stream concentration ("N") less than the de minimis concentration specified here, then this de minimis exemption does not apply to those provisions.

(f) Human Health,, Exposure, and Precautionary Statements. The following human health and environmental hazard and precautionary statements shall appear on each label as specified in paragraph (b) and the MSDS as specified in paragraph (c) of this section:

(1) Human health hazard statements. This substance may cause:

(i) skin irritation.

(ii) respiratory complications.

(iii) central nervous system effects.

(iv) internal organ effects.

(v) immune system effects.

(vi) developmental effects.

(2) Human hazard precautionary statements. When using this substance:

(i) avoid breathing the substance.

(ii) avoid ingestion.

(iii) use respiratory protection, or maintain workplace airborne concentrations at or below an 8-hour time-weighted average of 2.4 mg/m^3.

(3) The human hazard and precautionary statement on the label prepared pursuant to paragraph (b) of this section must be followed by the statement: "See the MSDS for details."

(g) Existing Hazard Communication Program. The Company need not take additional actions if existing programs and procedures satisfy the requirements of this section.

MANUFACTURING

(a)(1) Prohibition. The Company shall not cause, encourage, or suggest the manufacture (which includes import) of the PMN substance by any other person.

(2) Sunset Following SNUR. Subparagraph (a)(1) shall expire 75 days after promulgation of a final significant new use rule ("SNUR") governing the PMN substance under section 5(a)(2) of TSCA unless the Company is notified on or before that day of an action in a Federal Court seeking judicial review of the SNUR. If the Company is so notified, subparagraph (a)(1) shall not expire until EPA notifies the Company in writing that all Federal Court actions involving the SNUR have been resolved and the validity of the SNUR affirmed.

(3) Notice of SNUR. When EPA promulgates a final SNUR for the PMN substance and subparagraph (a)(1) expires in accordance with subparagraph (a)(2), the Company shall notify each person whom it causes, encourages or suggests to manufacture (which includes import) the PMN substance of the existence of the SNUR.

DISTRIBUTION

(a) Export Notice Requirement. No later than the date of distribution, the Company shall notify in writing any person to whom it distributes the PMN substance that, due to the issuance of this Consent Order under section 5(e) of TSCA, the PMN substance is subject to the export notification requirements of TSCA section 12(b) and 40 CFR Part 707 Subpart D. Such notice shall contain, in the form in which it appears in this Consent Order, the following information: (1) the PMN number, and (2) either (A) the specific chemical identity of the PMN substance, or (B) if the specific chemical identity is confidential, the generic chemical identity.

(b) Distribution Requirements. Except after the PMN has been completely reacted or as provided in paragraph (c), the Company shall distribute the PMN substance outside the Company, other than for disposal, only to a person who has agreed in writing prior to the date of distribution, to:

(1) Notify in writing any person to whom it distributes the PMN substance that, due to the issuance of this Consent Order under section 5(e) of TSCA, the PMN substance is subject to the export notification requirements of TSCA section 12(b) and 40 CFR Part 707 Subpart D. Such notice shall contain, in the form in which it appears in this Consent Order, the following information: (1) the PMN number, and (2) either (A) the specific chemical identity of the PMN substance, or (B) if the specific chemical identity is confidential, the generic chemical identity.

(2) Not further distribute the PMN substance to any other person, other than for disposal, until after the PMN substance has been completely reacted (cured).

(3) Comply with the same requirements and restrictions, if any, required of the Company in the Protection in the Workplace and the New Chemical Exposure Limit sections of this Order.

(4) Comply with the same requirements and restrictions, if any, required of the Company

in the Hazard Communication Program section of this Order.

(c) Temporary Transport and Storage. Notwithstanding paragraph (b), the Company may distribute the PMN substance outside the Company for temporary transport and storage in sealed containers provided the following three conditions are met:

(1) Subsequent to any such exempt temporary transport or storage of sealed containers, the PMN substance may be distributed only to the Company or a person who has given the Company the written agreement required by paragraph (b).

(2) Any human exposure or environmental release resulting from opening the sealed containers and removing or washing out the PMN substance may occur only while the PMN substance is in the possession and control of the Company or a person who has given the Company the written agreement required by paragraph (b).

(3) The sealed containers must be labeled in accordance with paragraph (b)(2) of the Hazard Communication Program section of this Order.

(d) Recipient Non-Compliance. If, at any time after commencing distribution in commerce of the PMN substance, the Company obtains knowledge that a recipient of the substance has failed to comply with any of the conditions specified in paragraph (b) of this Distribution section or, after subparagraph (b)(2) expires in accordance with subparagraph (e)(1), has engaged in a significant new use of the PMN substance (as defined in 40 CFR Part 721, Subpart E) without submitting a significant new use notice to EPA, the Company shall cease supplying the substance to that recipient, unless the Company is able to document each of the following:

(1) That the Company has, within 5 working days, notified the recipient in writing that the

recipient has failed to comply with any of the conditions specified in paragraph (b) of this Distribution section, or has engaged in a significant new use of the PMN substance without submitting a significant new use notice to EPA.

(2) That, within 15 working days of notifying the recipient of the noncompliance, the Company received from the recipient, in writing, a statement of assurance that the recipient is aware of the terms of paragraph (b) of this Distribution section and will comply with those terms, or is aware of the terms of the significant new use rule for the PMN substance and will not engage in a significant new use without submitting a significant new use notice to EPA.

(3) If, after receiving a statement of assurance from a recipient under subparagraph (d)(2) of this Distribution section, the Company obtains knowledge that the recipient has failed to comply with any of the conditions specified in paragraph (b) of this Distribution section, or has engaged in a significant new use of the PMN substance without submitting a significant new use notice to EPA, the Company shall cease supplying the PMN substance to that recipient, shall notify EPA of the failure to comply, and shall resume supplying the PMN substance to that recipient only upon written notification from the Agency.

(e) Sunset Following SNUR. (1) Subparagraph (b)(2) of this Distribution section shall expire 75 days after promulgation of a final SNUR for the PMN substance under section 5(a)(2) of TSCA, unless the Company is notified on or before that day of an action in a Federal Court seeking judicial review of the SNUR. If the Company is so notified, subparagraph (b)(2) of this Distribution section shall not expire until EPA notifies the Company in writing that all Federal Court actions involving the SNUR have been resolved and the validity of the SNUR affirmed.

(2) When EPA promulgates a final SNUR for the PMN substance and subparagraph (b)(2) of this

Distribution section expires in accordance with subparagraph (e)(1), the Company shall notify each person to whom it distributes the PMN substance of the existence of the SNUR. Such notification must be in writing and must specifically include all limitations contained in the SNUR which are defined as significant new uses, and which would invoke significant new use notification to EPA for the PMN substance. Such notice must also reference the publication of the SNUR for this PMN substance in either the Federal Register or the Code of Federal Regulations. After promulgation of a SNUR and expiration of subparagraph (b)(2), such notice may substitute for the written agreement required in the introductory clause of paragraph (b); so that, if the Company provides such notice to the persons to whom it distributes the PMN substance, then the Company is not required to obtain from such persons the written agreement specified in paragraph (b).

III. RECORDKEEPING

(a) Records. The Company shall maintain the following records until 5 years after the date they are created and shall make them available for inspection and copying by EPA in accordance with section 11 of TSCA:

(1) Exemptions. Records documenting that the PMN substance did in fact qualify for any one or more of the exemptions described in Section I, Paragraph (b) of this Order. Such records must satisfy all the statutory and regulatory recordkeeping requirements applicable to the exemption being claimed by the Company. Any amounts or batches of the PMN substance eligible for the export only exemption in Section I, Paragraph (b)(1) of this Order are exempt from all the requirements in this Recordkeeping section, if the Company maintains, for 5 years from the date of their creation, copies of the export label and export notice to EPA, required by TSCA sections 12(a)(1)(B) and 12(b), respectively. Any amounts or batches of the PMN substance

eligible for the research and development exemption in Section I, Paragraph (b)(2) of this Order are exempt from all the requirements in this Recordkeeping section, if the Company maintains, for 5 years from the date of their creation, the records required by 40 CFR 720.78(b). For any amounts or batches of the PMN substance claimed to be eligible for any other exemption described in Section I, Paragraph (b) of this Order, the Company shall keep records demonstrating qualification for that exemption as well as the records specified in paragraphs (2) and (3) below, but is exempt from the other recordkeeping requirements in this Recordkeeping section;

(2) Records documenting the manufacture (which includes import) volume of the PMN substance and the corresponding dates of manufacture (which includes import);

(3) Records documenting the names and addresses (including shipment destination address, if different) of all persons outside the site of manufacture (which includes import) to whom the Company directly sells or transfers the PMN substance, the date of each sale or transfer, and the quantity of the substance sold or transferred on such date;

(4) Records documenting the address of all sites of manufacture (which includes import), processing, and use;

(5) Records documenting establishment and implementation of a program for the use of any applicable personal protective equipment required pursuant to the Protection in the Workplace section of this Order;

(6) Records documenting the determinations required by the Protection in the Workplace section of this Order that chemical protective clothing is impervious to the PMN substance;

(7) Records required by paragraph (f). of the New Chemical Exposure Limits section of this Order, if applicable;

(8) Records documenting establishment and implementation of the hazard communication program required by the Hazard Communication Program section of this Order;

(9) Copies of labels required under the Hazard Communication Program section of this Order;

(10) Copies of Material Safety Data Sheets required by the Hazard Communication Program section of this Order;

(11) Records documenting compliance with any applicable manufacturing, processing, use, and distribution restrictions in the Manufacturing, Processing, Use, and Distribution sections of this Order, including distributees' written agreement to comply with the Distribution section of this Order;

(12) Copies of any Transfer Documents and notices required by the Successor Liability section of this Order, if applicable; and,

(13) The Company shall keep a copy of this Order at each of its sites where the PMN substance is manufactured (which includes import).

(b) Applicability. The provisions of this Recordkeeping Section are applicable only to activities of the Company and its Contract Manufacturer, if applicable, and not to activities of the Company's customers.

(c) OMB Control Number. Under the Paperwork Reduction Act and its regulations at 5 CFR Part 1320, particularly 5 CFR 1320.5(b), the Company is not required to respond to this "collection of information" unless this Order displays a currently valid control number from the Office of Management and Budget ("OMB"), and EPA so informs the Company. The "collection of

information" required in this TSCA §5(e) Consent Order has been approved under currently valid **OMB Control Number 2070-0012.**

IV. REQUESTS FOR PRE-INSPECTION INFORMATION

(a) EPA's Request for Information. Pursuant to section 11 of TSCA and 40 CFR 720.122, EPA may occasionally conduct on-site compliance inspections of Company facilities and conveyances associated with the PMN substance. To facilitate such inspections, EPA personnel may contact the Company in advance to request information pertinent to the scheduling and conduct of such inspections. Such requests may be written or oral. The types of information that EPA may request include, but are not limited to, the following:

(1) Expected dates and times when the PMN substance will be in production within the subsequent 12 months;

(2) Current workshift schedules for workers who are involved in activities associated with the PMN substance and may reasonably be exposed to the PMN substance;

(3) Current job titles or categories for workers who are involved in activities associated with the PMN substance and may reasonably be exposed to the PMN substance;

(4) Existing exposure monitoring data for workers who are involved in activities associated with the PMN substance and may reasonably be exposed to the PMN substance;

(5) Records required by the Recordkeeping section of this Order; and/or,

(6) Any other information reasonably related to determining compliance with this Order or conducting an inspection for that purpose.

(b) Company's Response. The Company shall respond to such requests within a reasonable period of time, but in no event later than 30 days after receiving EPA's request. When requested in writing by EPA, the Company's response shall be in writing. To the extent the information is known to or reasonably ascertainable by the Company at the time of the request, the Company's response shall demonstrate a good faith effort to provide reasonably accurate and detailed answers to all of EPA's requests.

(c) Confidential Business Information. Any Confidential Business Information ("CBI") that the Company submits to EPA pursuant to paragraph (b) shall be protected in accordance with §14 of TSCA and 40 CFR Part 2.

V. SUCCESSOR LIABILITY UPON TRANSFER OF CONSENT ORDER

(a) Scope. This section sets forth the procedures by which the Company's rights and obligations under this Order may be transferred when the Company transfers its interests in the PMN substance, including the right to manufacture (which includes import) the PMN substance, to another person outside the Company (the "Successor in Interest").

(b) Relation of Transfer Date to Notice of Commencement ("NOC").

(1) Before NOC. If the transfer from the Company to the Successor in Interest is effective before EPA receives a notice of commencement of manufacture (which includes import) ("NOC") for the PMN substance from the Company pursuant to 40 CFR 720.102, the Successor in Interest must submit a new PMN to EPA and comply fully with Section 5(a)(1) of TSCA and 40 CFR part 720 before commencing manufacture (which includes import) of the PMN substance.

(2) After NOC. If the transfer from the Company to the Successor in Interest is effective after EPA receives a NOC, the Successor in Interest shall comply with the terms of this Order and shall not be required to submit a new PMN to EPA.

(c) Definitions. The following definitions apply to this Successor Liability section of the Order:

(1) "Successor in Interest" means a person outside the Company who has acquired the Company's full interest in the rights to manufacture (which includes import) the PMN substance, including all ownership rights and legal liabilities, through a transfer document signed by the Company, as transferor, and the Successor in Interest, as transferee. The term excludes persons who acquire less than the full interest of the Company in the PMN substance, such as a licensee who has acquired a limited license to the patent or manufacturing rights associated with the PMN substance. A Successor in Interest must be incorporated, licensed, or doing business in the United States in accordance with 40 CFR 720.22(a)(3) and 40 CFR 720.3(z).

(2) "Transfer Document" means the legal instrument(s) used to convey the interests in the PMN substance, including the right to manufacture (which includes import) the PMN substance, from the Company to the Successor in Interest.

(d) Notices.

(1) Notice to Successor in Interest. On or before the effective date of the transfer, the Company shall provide to the Successor in Interest, by registered mail, a copy of the Consent Order and the "Notice of Transfer" document which is incorporated by reference as Attachment B to this Order.

(2) Notice to EPA. Within 10 business days of the effective date of the transfer, the Company shall, by registered mail, submit the fully executed Notice of Transfer document to: U.S. Environmental Protection Agency, New Chemicals Management Branch (7405), 1200 Pennsylvania Avenue, N.W., Washington, D.C. 20460.

(3) Transfer Document. Copies of the Transfer Document must be maintained by the Successor in Interest at its principal place of business, and at all sites where the PMN substance is manufactured (which includes import). Copies of the Transfer Document must also be made available for inspection pursuant to Section 11 of TSCA, must state the effective date of transfer, and must contain provisions which expressly transfer liability for the PMN substance under the terms of this Order from the Company to the Successor in Interest.

(e) Liability.

(1) The Company shall be liable for compliance with the requirements of this Order until the effective date of the transfer described above.

(2) The Successor in Interest shall be liable for compliance with the requirements of this Order effective as of the date of transfer.

(3) Nothing in this section shall be construed to prohibit the Agency from taking enforcement action against the Company after the effective date of the transfer for actions taken, or omissions made, during the time in which the Company manufactured (which includes import) processed, used, distributed in commerce, or disposed of the PMN substance pursuant to the terms of this Consent Order.

(f) Obligations to Submit Test Data under Consent Order. If paragraph (d) of the Testing section of this Consent Order requires the Company to submit test data to EPA at a specified production volume ("test trigger"), the aggregate volume of the PMN substance manufactured (which includes import) by the Company up to the date of transfer shall count towards the test trigger applicable to the Successor in Interest.

VI. MODIFICATION AND REVOCATION OF CONSENT ORDER

The Company may petition EPA at any time, based upon new information on the human health or environmental effects of, or human exposure to or environmental release of, the PMN substance, to modify or revoke substantive provisions of this Order. The exposures and risks identified by EPA during its review of the PMN substance and the information EPA determined to be necessary to evaluate those exposures and risks are described in the preamble to this Order. However, in determining whether to amend or revoke this Order, EPA will consider all relevant information available at the time the Agency makes that determination, including, where appropriate, any reassessment of the test data or other information that supports the findings in this Order, an examination of new test data or other information or analysis, and any other relevant information.

EPA will issue a modification or revocation if EPA determines that the activities proposed therein will not present an unreasonable risk of injury to health or the environment and will not result in significant or substantial human exposure or substantial environmental release in the absence of data sufficient to permit a reasoned evaluation of the health or environmental effects of the PMN substance.

In addition, the Company may petition EPA at any time to make other modifications to the language of this Order. EPA will issue such a modification if EPA determines that the modification is useful, appropriate, and consistent with the structure and intent of this Order as issued.

VII. EFFECT OF CONSENT ORDER

(a) Waiver. By consenting to the entry of this Order, the Company waives its rights to file objections to this Order pursuant to section 5(e)(1)(C) of TSCA, to receive service of this Order no later than 45 days before the end of the review period pursuant to section 5(e)(1)(B) of TSCA, and to challenge the validity of this Order in any subsequent action. Consenting to the entry of this Order, and agreeing to be bound by its terms, do not constitute an admission by the Company as to the facts or conclusions underlying the Agency's determinations in this proceeding. This waiver does not affect any other rights that the Company may have under TSCA.

(b) CBI Brackets. By signing this Order, the Company represents that it has carefully reviewed this document and hereby agrees that all information herein that is claimed as confidential by the Company (per section 14 of TSCA, 40 CFR Part 720 Subpart E, and 40 CFR Part 2) is correctly identified within brackets and that any information that is not bracketed is not claimed as confidential. To make this document available for public viewing, EPA will remove only the information contained within the brackets.

29 Jan 2015
Date

Maria J. Doa, Ph.D., Director
Chemical Control Division
Office of Pollution Prevention and Toxics

April 8, 2015
Date

[redacted]

ATTACHMENT A

DEFINITIONS

[Note: The attached Order may not contain some of the terms defined below.]

"Chemical name" means the scientific designation of a chemical substance in accordance with the nomenclature system developed by the Chemical Abstracts Service's rules of nomenclature, or a name which will clearly identify a chemical substance for the purpose of conducting a hazard evaluation.

"Chemical protective clothing" means items of clothing that provide a protective barrier to prevent dermal contact with chemical substances of concern. Examples can include, but are not limited to: full body protective clothing, boots, coveralls, gloves, jackets, and pants.

"Company" means the person or persons subject to this Order.

"Commercial use" means the use of a chemical substance or any mixture containing the chemical substance in a commercial enterprise providing saleable goods or a service to consumers (e.g., a commercial dry cleaning establishment or painting contractor).

"Common name" means any designation or identification such as code name, code number, trade name, brand name, or generic chemical name used to identify a chemical substance other than by its chemical name.

"Consumer" means a private individual who uses a chemical substance or any product containing the chemical substance in or around a permanent or temporary household or residence, during recreation, or for any personal use or enjoyment.

"Consumer product" means a chemical substance that is directly, or as part of a mixture, sold or made available to consumers for their use in or around a permanent or temporary household or residence, in or around a school, or in recreation.

"Container" means any bag, barrel, bottle, box, can, cylinder, drum, reaction vessel, storage tank, or the like that contains a hazardous chemical. For purposes of this section, pipes or piping systems, and engines, fuel tanks, or other operating systems in a vehicle, are not considered to be containers.

"Contract Manufacturer" means a person, outside the Company, who is authorized to manufacture (which includes import) the PMN substance under the conditions specified in Part II. of this Consent Order and in the Consent Order for Contract Manufacturer.

"Identity" means any chemical or common name used to identify a chemical substance or a mixture containing that substance.

"Immediate use." A chemical substance is for the "immediate use" of a person if it is under the control of, and used only by, the person who transferred it from a labeled container and will only be used by that person within the work shift in which it is transferred from the labeled container.

"Impervious." Chemical protective clothing is "impervious" to a chemical substance if the substance causes no chemical or mechanical degradation, permeation, or penetration of the chemical protective clothing under the conditions of, and the duration of, exposure.

"Manufacturing stream" means all reasonably anticipated transfer, flow, or disposal of a chemical substance, regardless of physical state or concentration, through all intended operations of manufacture, including the cleaning of equipment.

"MSDS" means material safety data sheet, the written listing of data for the chemical substance.

"NIOSH" means the National Institute for Occupational Safety and Health of the U.S. Department of Health and Human Services.

"Non-enclosed process" means any equipment system (such as an open-top reactor, storage tank, or mixing vessel) in which a chemical substance is manufactured (which includes import), processed, or otherwise used where significant direct contact of the bulk chemical substance and the workplace air may occur.

"Non-industrial use" means use other than at a facility where chemical substances or mixtures are manufactured (which includes import), or processed.

"PMN substance" means the chemical substance described in the Premanufacture notice submitted by the Company relevant to this Order.

"Personal protective equipment" means any chemical protective clothing or device placed on the body to prevent contact with, and exposure to, an identified chemical substance or substances in the work area. Examples include, but are not limited to, chemical protective clothing, aprons, hoods, chemical goggles, face splash shields, or equivalent eye protection, and various types of respirators. Barrier creams are not included in this definition.

"Process stream" means all reasonably anticipated transfer, flow, or disposal of a chemical substance, regardless of physical state or concentration, through all intended operations of processing, including the cleaning of equipment.

"Scientifically invalid" means any significant departure from the EPA-reviewed protocol or the Good Laboratory Practice Standards at 40 CFR Part 792 without prior or subsequent Agency review that prevents a reasoned evaluation of the health or environmental effects of the PMN substance.

"Scientifically equivocal data" means data which, although developed in apparent conformity with the Good Laboratory Practice Standards and EPA-reviewed protocols, are inconclusive, internally inconsistent, or otherwise insufficient to permit a reasoned evaluation of the potential risk of injury to human health or the environment of the PMN substance.

"Sealed container" means a closed container that is physically and chemically suitable for long-term containment of the PMN substance, and from which there will be no human exposure to, nor environmental release of, the PMN substance during transport and storage.

"Use stream" means all reasonably anticipated transfer, flow, or disposal of a chemical substance, regardless of physical state or concentration, through all intended operations of industrial, commercial, or consumer use.

"Waters of the United States" has the meaning set forth in 40 CFR 122.2.

"Work area" means a room or defined space in a workplace where the PMN substance is manufactured (which includes import), processed, or used and where employees are present.

"Workplace" means an establishment at one geographic location containing one or more work areas.

ATTACHMENT B

NOTICE OF TRANSFER
OF
TOXIC SUBSTANCES CONTROL ACT
SECTION 5(e) CONSENT ORDER

_____ _____
Company (Transferor) PMN Number

1. Transfer of Manufacture (which includes import) Rights. Effective on _____, the Company did sell or otherwise transfer to _____, ("Successor in Interest") the rights and liabilities associated with manufacture (which includes import) of the above-referenced chemical substance, which was the subject of a premanufacture notice ("PMN") and is governed by a Consent Order issued by the U.S. Environmental Protection Agency ("EPA") under the authority of §5(e) of the Toxic Substances Control Act ("TSCA," 15 U.S.C. §2604(e)).

2. Assumption of Liability. The Successor in Interest hereby certifies that, as of the effective date of transfer, all actions or omissions governed by the applicable Consent Order limiting manufacture (which includes import), processing, use, distribution in commerce and disposal of the PMN substance, shall be the responsibility of the Successor in Interest. Successor in Interest also certifies that it is incorporated, licensed, or doing business in the United States in accordance with 40 CFR 720.22(a)(3).

3. Confidential Business Information. The Successor in Interest hereby:

___ reasserts,

___ relinquishes, or

___ modifies

all Confidential Business Information ("CBI") claims made by the Company, pursuant to Section 14 of TSCA and 40 CFR part 2, for the PMN substance(s). Where "reasserts" or "relinquishes" is indicated, that designation shall be deemed to apply to all such claims. Where "modifies" is indicated, such modification shall be explained in detail in an attachment to this Notice of Transfer. Information which has been previously disclosed to the public (e.g., a chemical identity that was not claimed as CBI by the original submitter) would not subsequently be eligible for confidential treatment under this Notice of Transfer.

NOTICE OF TRANSFER OF
TOXIC SUBSTANCES CONTROL ACT
SECTION 5(e) CONSENT ORDER

(continued)

Company (Transferor)	PMN Number
Signature of Authorized Official	Date
Printed Name of Authorized Official	
Title of Authorized Official	
Successor in Interest	
Signature of Authorized Official	Date
Printed Name of Authorized Official	
Title of Authorized Official	
Address	
City, State, Zip Code	

NOTICE OF TRANSFER OF
TOXIC SUBSTANCES CONTROL ACT
SECTION 5(e) CONSENT ORDER
(continued)

_____
Successor's Technical Contact

_____
Address

_____
City, State, Zip Code

_____
Phone

Company Sanitized

PMN2010P1

PMN Page 1

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SANITIZED SUBMISSION

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11 JAN -4 PM 2:05

Form Approved. O.M.B. Nos. 2070-0012 and 2070-0038

U.S. ENVIRONMENTAL PROTECTION AGENCY

AGENCY USE ONLY

Date of receipt: 1-4-11

11 JAN -4 PM 2:05

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When completed, send this form to:

Off
Do
US
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Contact Numbers: 202-564-8930/8940

Submission Report Number

TSB2101224041049680

Total Number of Pages	User Fee Payment ID Number	TS Number
344	0325025194	B2K343

GENERAL INSTRUCTIONS

- You must provide all information requested in this form to the extent that it is known to or reasonably ascertainable by you. Make reasonable estimates if you do not have actual data.
- Before you complete this form, you should read the "Instructions Manual for Premanufacture Notification" (the Instructions Manual is available from the Toxic Substances Control Act (TSCA) Information Service by calling 202-554-1404, or faxing 202-554-5603).
- If a user fee has been remitted for this notice (40 CFR 700.45), indicate in the boxes above the TS-user fee identification number you have generated. Remember, your user fee ID number must also appear on your corresponding fee remittance. For mailing address information see the Help instructions in the e-PMN tool.

Part I – GENERAL INFORMATION

You must provide the currently correct Chemical Abstracts (CA) Name of the new chemical substance, even if you claim the identity as confidential. You may authorize another person to submit chemical identity information for you, but your submission will not be complete and the review will not begin until EPA receives this information. A letter in support of your submission should reference your TS user fee identification number. For all Section 5 Notice submissions (paper or electronic) you must submit an original notice including all test data; if you claimed any information as confidential, an original sanitized copy must also be submitted.

Part II – HUMAN EXPOSURE AND ENVIRONMENTAL RELEASE

If there are several manufacture, processing, or use operations to be described in Part II, sections A and B of this notice, reproduce the sections as needed.

Part III – LIST OF ATTACHMENTS

For paper submissions, attach additional sheets if there is not enough space to answer a question fully. Label each continuation sheet with the corresponding section heading. In Part III, list these attachments, any test data or other data and any optional information included in the notice.

OPTIONAL INFORMATION

You may include any information that you want EPA to consider in evaluating the new substance. On page 11 of this form, space has been provided for you to describe pollution prevention and recycling information you may have regarding the new substance. "Binding" boxes are included throughout this form for you to indicate your willingness to be bound to certain statements you make in this section, such as use, production volume, protective equipment . . . The intention is to reduce delays that routinely accompany the development of consent orders or Significant New Use Rules. Checking a "binding" box in a PMN does not by itself prohibit the submitter from later deviating from the information (except chemical identity) reported in the form; however, in the case of exemption applications (such as TMEA, LVE, LOREX) certain information provided in such notifications is binding on the submitter when the Agency approves the exemption application, especially if the production volume "binding" box is chosen in a LVE.

CONFIDENTIALITY CLAIMS

You may claim any information in this notice as confidential. To assert a claim on the form, mark (X) the confidential box next to the information that you claim as confidential. To assert a claim in an attachment, circle or bracket the information you claim as confidential. If you claim information in the notices as confidential, you must also provide a sanitized version of the notice, (including attachments). For additional instructions on claiming information as confidential, read the Instructions Manual.

TEST DATA AND OTHER DATA

You are required to submit all test data in your possession or control and to provide a description of all other data known to or reasonably ascertainable by you, if these data are related to the health and environmental effects on the manufacture, processing, distribution in commerce, use, or disposal of the new chemical substance. Standard literature citations may be submitted for data in the open scientific literature. Complete test data (written in English), not summaries of data, must be submitted if they do not appear in the open literature. You should clearly identify whether test data is on the substance or on an analog. Also, the chemical composition of the tested material should be characterized. Following are examples of test data and other data. Data should be submitted according to the requirements of §720.50 of the Premanufacture Notification Rule (40 CFR Part 720).

Test Data (Check Below any included in this notice)

[X]	Environmental fate data	[ ]	Other Data
[X]	Health effects data	[ ]	Risk Assessments
[X]	Environmental effects data	[ ]	Structure/activity relationships
[X]	Physical/Chemical Properties (A physical and chemical properties worksheet is located on the last page of this form.)		
[ ]	Test data not in the possession or control of the submitter		

TYPE OF NOTICE (Check Only One)

Received
OPPT NCIC
2/3/2011

- [X] **PMN** (Premanufacture Notice)
- [ ] **SNUN** (Significant New Use Notice)
- [ ] **TMEA** (Test Marketing Exemption Application)
- [ ] **LVE** (Low Volume Exemption) @ 40 CFR 723.50(c)(1)
- [ ] **LOREX** (Low Release/Low Exposure Exemption) @ 40 CFR 723.50(c)(2)
- [ ] **LVE** Modification
- [ ] **LOREX** Modification
- [ ] **Mock Submission**
- [ ] Mark (X) if pending Letter of Support

IS THIS A CONSOLIDATED PMN (Y/N)? ____

# of chemicals or polymers (Prenotice Communication # required, enter # on p. 3). ____

- [X] Mark (X) if any information in this notice is claimed as confidential.

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The public reporting and recordkeeping burden for this collection of information is estimated to average 93 hours per response. Send comments on the Agency's need for this information, the accuracy of the provided burden estimates, and any suggested methods for minimizing respondent burden, including through the use of automated collection techniques to the Director, Collection Strategies Division, U.S. Environmental Protection Agency (2822T), 1200 Pennsylvania Ave., NW, Washington, D.C. 20460. Include the OMB control number in any correspondence. Do not send the completed EPA Form 7710-25 to this address.

CERTIFICATION -- A printed copy of this signature page, with original signature, must be submitted with CD or paper submission.

I certify that to the best of my knowledge and belief:

1. The company named in Part I, section A, subsection 1a of this notice form intends to manufacture, import or process for a commercial purpose, other than in small quantities solely for research and development, the substance identified in Part I, Section B.
2. All information provided in this notice is complete and truthful as of the date of submission.
3. I am submitting with this notice all test data in my possession or control and a description of all other data known to or reasonably ascertainable by me as required by §720.50 of the Premanufacture Notification Rule.

Additional Certification Statements:

If you are submitting a PMN, Intermediate PMN, Consolidated PMN, or SNUN, check the following **user fee** certification statement that applies:

- [X] The Company named in Part I, Section A has remitted the fee of $2500 specified in 40 CFR 700.45(b), or
- [ ] The Company named in Part I, Section A has remitted the fee of $1000 for an Intermediate PMN (defined @ 40 CFR 700.43) in accordance with 40 CFR 700.45(b), or
- [ ] The Company named in Part I Section A is a small business concern under 40 CFR 700.43 and has remitted a fee of $100 in accordance with 40 CFR 700.45(b).

If you are submitting a **Low Volume Exemption (LVE)** application in accordance with 40 CFR 723.50(c)(1) or a **Low Release and Low Exposure Exemption (LoRex)** application in accordance with 40 CFR 723.50(c)(2), check the following certification statements:

- [ ] The manufacturer submitting this notice intends to manufacture or import the new chemical substance for commercial purposes, other than in small quantities solely for research and development, under the terms of 40 CFR 723.50.
- [ ] The manufacturer is familiar with the terms of this section and will comply with those terms; and
- [ ] The new chemical substance for which the notice is submitted meets all applicable exemption conditions.
- [ ] If this application is for an LVE in accordance with 40 CFR 723.50(c)(1), the manufacturer intends to commence manufacture of the exempted substance for commercial purposes within 1 year of the date of the expiration of the 30 day review period.

The accuracy of the statements you make in this notice should reflect your best prediction of the anticipated facts regarding the chemical substance described herein. Any knowing and willful misrepresentation is subject to criminal penalty pursuant to 18 USC 1001.				Confidential
Signature and title of Authorized Official (Original Signature Required)		Date		[X]

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Part I -- GENERAL INFORMATION

Section A – SUBMITTER IDENTIFICATION

Mark (X) the "Confidential" box next to any subsection you claim as confidential

1a. Person Submitting Notice (in U.S.)					Confidential
Name of Authorized Official	(first) XXX		(last) XXX		
Position	XXX				
Company	XXX				X
Mailing Address (number & street)	XXX				
City	XXX	State		Postal Code	XXX
email	XXX				

b. Agent (if Applicable)					Confidential
Name of Authorized Official	(first)		(last)		
Position					
Company					
Mailing Address (number & street)					☐
City		State		Postal Code	
e-mail		Telephone (include area code)			

c. Joint Submitter (if applicable)					Confidential
If you are submitting this notice as part of a joint submission, mark (X)				☐	
Name of Authorized Official	(first)		(last)		
Position					
Company					☐
Mailing Address (number & street)					
City		State		Postal Code	
e-mail		Telephone (include area code)			

2. Technical Contact (in U.S.)					Confidential
Name of Authorized Official	(first) XXX		(last) XXX		
Position	XXX				
Company	XXX				X
Mailing Address (number & street)	XXX				
City	XXX	State		Postal Code	XXX
e-mail	XXX	Telephone (include area code)			XXX

			Mark (X) if none	Confidential
3.	If you have had a prenotice communication (PC) concerning this notice and EPA assigned a PC Number to the notice, enter the number.		X	☐
4.	If you previously submitted an exemption application for the chemical substance covered by this notice, enter the exemption number assigned by EPA. If you previously submitted a PMN for this substance enter the PMN number assigned by EPA (i.e. withdrawn or incomplete).		X	☐
5.	If you have submitted a notice of Bona fide intent to manufacture or import for the chemical substance covered by this notice, enter the notice number assigned by EPA.		X	☐

6. Type of Notice – Mark (X)						
1.	Manufacture Only ☐ Binding Option ☐	2.	Import Only X Binding Option ☐	3.	Both ☐	

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Part I – GENERAL INFORMATION -- Continued

Section B – CHEMICAL IDENTITY INFORMATION:	You must provide a currently correct Chemical Abstracts (CA) name of the substance based on current CA index nomenclature rules and conventions.

Mark (X) the "Confidential" box next to any item you claim as confidential

Complete either item 1 (Class 1 or 2 substances) or 2 (Polymers) as appropriate. Complete all other items.

If another person will submit chemical identity information for you (for either Item 1 or 2), mark (X) the box at the right. Identify the name, company, and address of that person in a continuation sheet.			☐
1. Class 1 or 2 chemical substances (for definitions of class 1 and class 2 substances, see the Instructions Manual)	Class 1	Class 2	CBI
a. Class of substance - Mark (X)	☐	☐	☒

b. Chemical name (Currently correct Chemical Abstracts (CA) Name that is consistent with TSCA Inventory listings for similar substances. For Class 1 substances a CA Index Name must be provided. For Class 2 substances either a CA Index Name or CA Preferred Name must be provided, which ever is appropriate based on current CA index nomenclature rules and conventions). ☒

XXX

CAS Registry Number (if a number already exists for the substance)	XXX

c. Please identify which method you used to develop or obtain the specified chemical identity information reported in this notice: (check one).

Method 1 (CAS Inventory Expert Service - a copy of the Identification report obtained from the CAS Inventory Expert Services must be submitted as an attachment to this notice)	☒	IES Order Number	152463	**Method 2** (Other Source)	☐
Enter Attachment filename for Part I, Section B, 1. c.					☐

d. Molecular formula	XXX	☒
e. For a class 1 substance, provide a complete and correct chemical structure diagram. For a class 2 substance, provide a correct representative or partial chemical structure diagram, as complete as can be known, if one can be reasonably ascertained.		☐

Enter Attachment filename for Part I, Section B, 1. e.	☐

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For a class 2 substance - (1) List the immediate precursor substances with their respective CAS Registry Numbers. (2) Describe the nature of the reaction or process. (3) Indicate the range of composition and the typical composition (where appropriate).	Confidential
e. (1) List the immediate precursor substance names with their respective CAS Registry Numbers.	☐
Enter Attachment filename for Part I, Section B, 1. e. (1)	☐
e. (2) Describe the nature of the reaction or process.	☐
Enter Attachment filename for Part I, Section B, 1. e. (2)	☐
e. (3) Indicate the range of composition and the typical composition (where appropriate).	☐
Enter Attachment filename for Part I, Section B, 1. e. (3)	☐

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Part I -- GENERAL INFORMATION – Continued

Section B -- CHEMICAL IDENTITY INFORMATION -- Continued

2. Polymers (For a definition of polymer, see the Instructions Manual.)	Confidential
a. Indicate the number-average weight of the lowest molecular weight composition of the polymer you intend to manufacture. Indicate maximum weight percent of low molecular weight species (not including residual monomers, reactants, or solvents) below 500 and below 1,000 absolute molecular weight of that composition.	☐

Describe the methods of measurement or the basis for your estimates:

GPC ☐	**Other** (Specify Below) ☐

Specify Other:

(i) lowest number average molecular weight:	(ii) maximum weight % below 500 molecular weight:	(iii) maximum weight % below 1000 molecular weight:

Enter Attachment filename for Part I, Section B, 2. a. ☐

b. You must make separate confidentiality claims for monomer or other reactant identity, composition information, and residual information. Mark (X) the "Confidential" box next to any item you claim as confidential

(1) - Provide the specific chemical name and CAS Registry Number (if a number exists) of each monomer or other reactant used in the manufacture of the polymer.
(2) - Mark (X) this column if entry in column (1) is confidential.
(3) - Indicate the typical weight percent of each monomer or other reactant in the polymer.
(4) - Choose "yes" from drop down menu if you want a monomer or other reactant used at two weight percent or less to be listed as part of the polymer description on the TSCA Chemical Substance Inventory.
(5) - Mark (X) this column if entries in columns (3) and (4) are confidential.
(6) - Indicate the maximum weight percent of each monomer or other reactant that may be present as a residual in the polymer as manufactured for commercial purposes.
(7) - Mark (X) this column if entry in column (6) is confidential.

Monomer or other reactant specific chemical name (1)	CBI (2)	Typical composition (3)	Include in identity (4)	CBI (5)	Max residual (6)	CBI (7)
CAS Registry Number (1)						
CAS Registry Number (1)						
CAS Registry Number (1)						
CAS Registry Number (1)						
CAS Registry Number (1)						

Mark (X) this box if the data continues on the next page. ☐

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c. Please identify which method you used to develop or obtain the specified chemical identity information reported in this notice (check one).				CBI
Method 1 (CAS Inventory Expert Service - a copy of the identification report obtained from CAS Inventory Expert Service must be submitted as an attachment to this notice) ☐	IES Order Number		**Method 2** (other source) ☐	
Enter Attachment filename for Part I, Section B, 2. c.				☐

d. The currently correct Chemical Abstracts (CA) name for the polymer that is consistent with TSCA Inventory listings for similar polymers.	☐
CAS Registry Number (if a number already exists for the substance)	

e. Provide a correct representative or partial chemical structure diagram, as complete as can be known, if one can be reasonably ascertained.	☐
Enter Attachment filename for Part I, Section B, 2. e.	☐

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Part I -- GENERAL INFORMATION -- Continued

Section B -- CHEMICAL IDENTITY INFORMATION -- Continued

3. Impurities
   (a) - Identify each impurity that may be reasonably anticipated to be present in the chemical substance as manufactured for commercial purpose. Provide the CAS Registry Number if available. If there are unidentified impurities, enter "unidentified."
   (b) - Estimate the maximum weight % of each impurity. If there are unidentified impurities, estimate their total weight %.

Impurity (a)	CAS Registry Number (a)	Maximum Percent % (b)	Confi-dential
XXX	XXX	XXX	X

Mark (X) this box if the data continues on the next page. ☐

Enter Attachment filename for Part I, Section B, 3. ☐

4. Synonyms - Enter any chemical synonyms for the new chemical identified in subsection 1 or 2.
XXX ☒

Enter Attachment filename for Part I, Section B, 4. ☐

5. Trade identification - List trade names for the new chemical substance identified in subsection 1 or 2. ☐

Enter Attachment filename for Part I, Section B, 5. ☐

6. Generic chemical name - If you claim chemical identify as confidential, you must provide a generic name for your substance that reveals the specific chemical identity of the new chemical substance to the maximum extent possible. Refer to the TSCA Chemical Substance Inventory, 1985 Edition, Appendix B for guidance on developing generic names.

Alkali transition metal oxide

Enter Attachment filename for Part I, Section B, 6.

7. Byproducts - Describe any byproducts resulting from the manufacture, processing, use, or disposal of the new chemical substance. Provide the CAS Registry Number if available.

Byproduct (1)	CAS Registry Number (2)	Confi-dential

Mark (X) this box if the data continues on the next page. ☐

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Part I -- GENERAL INFORMATION -- Continued

Section C -- PRODUCTION, IMPORT, AND USE INFORMATION:

The information on this page refers to consolidated chemical number(s): ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

Mark (X) the "Confidential" box next to any item you claim as confidential.

1. Production volume -- Estimate the **maximum** production volume during the first 12 months of production. Also estimate the maximum production volume for any consecutive 12-month period during the first three years of production. Estimates should be on 100% new chemical substance basis. For a Low Volume Exemption application, if you choose to have your notice reviewed at a lower production volume than 10,000 kg/yr, specify the volume and mark (x) in the binding box. If granted, you are bound to this volume.

Maximum first 12-month production (kg/yr) (100% new chemical substance basis)	Maximum 12-month production (kg/yr) (100% new chemical substance basis)	Confidential	Binding Option Mark (X)
XXX	XXX	X	☐

Enter Attachment filename for Part I, Section C, 1.		CBI ☐

2. Use Information -- You must make separate confidentiality claims for the description of the category of use, the percent of production volume devoted to each category, the formulation of the new substance, and other use information. Mark (X) the "Confidential" Box next to any item you claim as confidential.

a. (1) --Describe each intended category of use of the new chemical substance by function and application.
(2) --Mark (X) this column if entry column (1) is confidential business information (CBI).
(3) --Indicate your willingness to have the information provided in column (1) binding.
(4) --Estimate the percent of total production for the first three years devoted to each category of use.
(5) --Mark (X) this column if entry in column (4) is confidential business information (CBI).
(6) --Estimate the percent of the new substance as formulated in mixtures, suspensions, emulsions, solutions, or gels as manufactured for commercial purposes at sites under your control associated with each category of use.
(7) --Mark (X) this column if entry in column (6) is confidential business information (CBI).
(8) --Indicate % of product volume expected for the listed "use" sectors. Mark more than one box if appropriate. Mark (X) to indicate your willingness to have the use type provided in (8) binding.
(9) --Mark (X) this column if entry(ies) in column (8) is (are) confidential business information (CBI).

Category of use (1) (by function and application i.e. a dispersive dye for finishing polyester fibers)	CBI (2)	Binding Option Mark (X) (3)	Production % (4)	CBI (5)	% in Formulation (6)	CBI (7)	% of substance expected per use (8)					CBI (9)
							Site-limited	Consumer*	Industrial	Commercial	Binding Option	
XXX	X		XXX	X	XXX	X	XXX	XXX	XXX	XXX		X

* If you have identified a "consumer" use, please provide on a continuation sheet a detailed description of the use(s) of this chemical substance in consumer products. In addition include estimates of the concentration of the new chemical substance as expected in consumer products and describe the chemical reactions by which this substance loses its identity in the consumer product.

Mark (X) this box if the data continues on the next page. ☐

b. Generic use description — If you claim any category of use description in subsection 2a as confidential, enter a generic description of that category. Read the Instruction Manual for examples of generic use descriptions.

Battery Materials

Enter Attachment filename for Part I, Section C, 2. b.		CBI ☐

3. Hazard Information -- Include in the notice a copy of reasonable facsimile of any hazard warning statement, label, material safety data sheet, or other information which will be provided to any person who is reasonably likely to be exposed to this substance regarding protective equipment or practices for the safe handing, transport, use, or disposal of the new substance. List in part III hazard information you include.

Mark (X) this box if you attach hazard information.	X	Binding Option Mark (X) ☐

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Part II-- HUMAN EXPOSURE AND ENVIRONMENTAL RELEASE

Section A -- INDUSTRIAL SITES CONTROLLED BY THE SUBMITTER

Mark (X) the "Confidential" box next to any item you claim as confidential

The information on pages 8 and 8a refer to consolidated chemical number(s): ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

Complete section A for each type of manufacture, processing, or use operation involving the new chemical substance at industrial sites you control. Importers do not have to complete this section for operations outside the U.S.; however, you may still have reporting requirements if there are further industrial processing or use operations after import. You must describe these operations. See instructions manual

1. Operation description

a. Identity -- Enter the identity of the site at which the operation will occur.

				Confi-dential
Name				☐
Site address (number and street)				
City		County		
State		ZIP code		

If the same operation will occur at more than one site, enter the number of sites. Identify the additional sites on a continuation sheet, and if any of the sites have significantly different production rates or operations, include all the information requested in this section for those sites as attachments. → ☐

Mark (X) this box if the data continues on the next page. ☐

b. Type -- Mark (X) Manufacturing ☐ Processing ☐ Use ☐ ☐

c. Amount and Duration -- Complete 1 or 2 as appropriate

				Confi-dential
1. Batch	Maximum kg/batch (100% new chemical substance)	Hours/batch	Batches/year	☐
2. Continuous	Maximum kg/day (100% new chemical substance)	Hours/day	Days/year	☐

d. Process description — Mark (X) to indicate your willingness to have your process description binding. → ☐

(1) Diagram the major unit operation steps and chemical conversions. Include interim storage and transport containers (specify- e.g. 5 gallon pails, 55 gallon drum, rail car, tank truck, etc.).

(2) Provide the identity, the approximate weight (by kg/day or kg/batch on a 100% new chemical substance basis), and entry point of all starting materials and feedstocks (including reactants, solvents, catalysts, etc.), and of all products, recycle streams, and wastes. Include cleaning chemicals (note frequency if not used daily or per batch.).

(3) Identify by number the points of release, including small or intermittent releases, to the environment of the new chemical substance. If releasing to two media at the same step, assign a second release number for the second medium.

☐

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Diagram of the major unit operation steps.	Confidential ☐

Enter Attachment filename for Part II, Section A, 1. d.	☐

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Part II-- HUMAN EXPOSURE AND ENVIRONMENTAL RELEASE -- Continued

Section A -- INDUSTRIAL SITES CONTROLLED BY THE SUBMITTER -- Continued

The information on pages 9 and 9a refer to consolidated chemical number(s): ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

2. Occupational Exposure -- You must make separate confidentiality claims for the description of worker activity, physical form of the new chemical substance, number of workers exposed, and duration of activity. Mark (X) the "Confidential" box next to any item you claim as confidential.

(1) -- Describe the activities (i.e. bag dumping, tote filling, unloading drums, sampling, cleaning, etc.) in which workers may be exposed to the substance.
(2) -- Mark (X) this column if entry in column (1) is confidential business information (CBI).
(3) -- Describe any protective equipment and engineering controls used to protect workers.
(4) and (6) -- Indicate your willingness to have the information provided in column (3) or (5) binding.
(5) -- Indicate the physical form(s) of the new chemical substance (e.g., solid: crystal, granule, powder, or dust) and % new chemical substance (if part of a mixture) at the time of exposure.
(7) -- Mark (X) this column if entries in columns (3) and (5) are confidential business information (CBI).
(8) -- Estimate the maximum number of workers involved in each activity for all sites combined.
(9) -- Mark (X) this column if entry in column (8) is confidential business information (CBI).
(10) and (11) -- Estimate the maximum duration of the activity for any worker in hours per day and days per year.
(12) -- Mark (X) this column if entries in columns (10) and (11) are confidential business information (CBI).

Worker activity (i.e., bag dumping, filling drums) (1)	CBI (2)	Protective Equipment/ Engineering Controls (3)	Binding Option Mark (X) (4)	Physical form(s) & % new substance (5)	Binding Option Mark (X) (6)	CBI (7)	# of Workers Exposed (8)	CBI (9)	Maximum Duration		CBI (12)
									Hrs/Day (10)	Days/Yr (11)	

Mark (X) this box if the data continues on the next page. ☐

Enter Attachment filename for Part II, Section A on the bottom of page 9a. ☐

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PMN Page 9a

3. Environmental Release and Disposal -- You must make separate confidentiality claims for the release number and the amount of the new chemical substance released and other release and disposal information. Mark (X) the "Confidential" box next to each item you claim as confidential.

(1) -- Enter the number of each release point identified in the process description, part II, section A, subsection 1d(3).
(2) -- Estimate the amount of the new substance released (a) directly to the environment or (b) into control technology (in kg/day or kg/batch).
(3) -- Mark (X) this column if entries in columns (1) and (2) are confidential business information (CBI).
(4) -- Identify the media (stack air, fugitive air (optional-see Instruction Manual), surface water, on-site or off-site land or incineration, POTW, or other (specify)) to which the new substance will be released from that release point.
(5) -- a. Describe control technology, if any, and control efficiency that will be used to limit the release of the new substance to the environment. For releases disposed of on land, characterize the disposal method and state whether it is approved for disposal of RCRA hazardous waste. On a continuation sheet, for each site describe any additional disposal methods that will be used and whether the waste is subject to secondary or tertiary on-site treatment. b. Estimate the amount released to the environment after control technology (in kg/day).
(6) -- Mark (X) this column if entries in columns (4) and (5) are confidential business information (CBI).
(7) -- Identify the destination(s) of releases to water. Please supply NPDES (National Pollutant Discharge Elimination System) numbers for direct discharges or NPDES numbers of the POTW (Publicly Owned Treatment Works). Mark (X) if the POTW name or NPDES # is confidential business information (CBI).

Release Number	Amount of New Substance Released		CBI	Medium of release e.g. Stack air	Control technology and efficiency (you may wish to optionally attach efficiency data)			CBI
(1)	(2a)	(2b)	(3)	(4)	(5a)	Binding Mark (X)	(5b)	(6)

Mark (X) this box if the data continues on the next page. ☐

(7) Mark (X) the destination(s) of releases to water.		NPDES#	CBI
☐ POTW--provide name(s)			☐
☐ Navigable waterway- - provide name(s)			☐
☐ Other--Specify			☐

Enter Attachment filename for Part II, Section A. ☐

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PMN Page 10

Part II-- HUMAN EXPOSURE AND ENVIRONMENTAL RELEASE – Continued

Section B -- INDUSTRIAL SITES CONTROLLED BY OTHERS

The information on pages 10 and 10a refer to consolidated chemical number(s): ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

Complete section B for typical processing or use operations involving the new chemical substance at sites you do not control. Importers do not have to complete this section for operations outside the U.S.; however, you must report any processing or use activities after import. See the Instructions Manual. *Complete a separate section B for each type of processing, or use operation involving the new chemical substance.* If the same operation is performed at more than one site describe the typical operation common to these sites. Identify additional sites on a continuation sheet.

1(a). Operation Description -- To claim information in this section as confidential, bracket (e.g. {}) the specific information that you claim as confidential.

(1) -- Diagram the major unit operation steps and chemical conversions, including interim storage and transport containers (specify - e.g. 5 gallon pails, 55 gallon drums, rail cars, tank trucks, etc). On the diagram, identify by letter and briefly describe each worker activity.

(2) -- Either in the diagram or in the text field 1(b) below, provide the identity, the approximate weight (by kg/day or kg/batch, on an 100% new chemical substance basis), and entry point of all feedstocks (including reactants, solvents and catalysts, etc) and all products, recycle streams, and wastes. Include cleaning chemicals (note frequency if not used daily or per batch).

(3) -- Either in the diagram or in the text field 1(b) below, identify by number the points of release, including small or intermittent releases, to the environment of the new chemical substance.

(4) -- Please enter the # of sites (remember to identify the locations of these sites on a continuation sheet):

	Number of Sites		Confidential ☒

1(b). (Optional) This space is for a text description to clarify the diagram above. Confidential ☐

Enter Attachment filename for Part II, Section B on the bottom of page 10a.		☐

PMN2010P10A

SANITIZED SUBMISSION

PMN Page 10a

2. Worker Exposure/Environmental Release

(1) -- From the diagram above, provide the letter for each worker activity. Complete 2-8 for each worker activity described.
(2) -- Estimate the number of workers exposed for all sites combined.
(4) -- Estimate the typical duration of exposure per worker in (a) hours per day and (b) days per year.
(6) -- Describe physical form of exposure and % new chemical substance (if in mixture), and any protective equipment and engineering controls, if any, used to protect workers.
(7) -- Estimate the percent of the new substance as formulated when packaged or used as a final product.
(9) -- From the process diagram above, enter the number of each release point. Complete 9-13 for each release point identified.
(10) -- Estimate the amount of the new substance released (a) directly to the environment or (b) into control technology to the environment (in kg/day or kg/batch).
(12) -- Describe media of release i.e. stack air, fugitive air (optional-see Instructions Manual), surface water, on-site or off-site land or incineration, POTW, or other (specify) and control technology, if any, that will be used to limit the release of the new substance to the environment.
(14) -- Identify byproducts which may result from the operation.
(3), (5), (8), (11), (13) and (15) -- Mark (X) this column if any of the proceeding entries are confidential business information (CBI).

Letter of Activity	# of Workers Exposed	CBI	Duration of Exposure		CBI	Protective Equip./Engineering Controls/Physical Form	% new substance	% in Formulation	CBI
(1)	(2)	(3)	(4a)	(4b)	(5)	(6)	(6)	(7)	(8)
XXX	XXX	X	XXX	XXX	X	XXX	XXX	XXX	X

Release Number	Amount of New Substance Released		CBI	Media of Release & Control Technology	CBI
(9)	(10a)	(10b)	(11)	(12)	(13)
XXX	XXX	XXX	X	XXX	X

Mark (X) this box if the data continues on the next page. ☐

(14) Byproducts: | **(15) CBI** ☐

Enter Attachment filename for Part II, Section B. ☐

PMN2010P11

SANITIZED SUBMISSION

PMN Page 11

OPTIONAL POLLUTION PREVENTION INFORMATION

To claim information in the following section as confidential, bracket (e.g. {}) the specific information that you claim as confidential.

In this section you may provide information not reported elsewhere in this form regarding your efforts to reduce or minimize potential risks associated with activities surrounding manufacturing, processing, use and disposal of the PMN substance. Please include new information pertinent to pollution prevention, including source reduction, recycling activities and safer processes or products available due to the new chemical substance. Source reduction includes the reduction in the amount or toxicity of chemical wastes by technological modification, process and procedure modification, product reformulation, and/or raw materials substitution. Recycling refers to the reclamation of useful chemical components from wastes that would otherwise be treated or released as air emissions or water discharges, or land disposal. Quantitative or qualitative descriptions of pollution prevention, source reduction and recycling should emphasize potential risk reduction in addition to compliance with existing regulatory requirements. The EPA is interested in the information to assess overall net reductions in toxicity or environmental releases and exposures, not the shifting of risks to other media (e.g., air to water) or nonenvironmental areas (e.g., occupational or consumer exposure). To the extent known, information about the technology being replaced will assist EPA in its relative risk determination. In addition, information on the relative cost or performance characteristics of the PMN substance to potential alternatives may be provided.

Describe the expected net benefits, such as

(1) an overall reduction in risk to human health or the environment;
(2) a reduction in the generation of waste materials through recycling, source reduction or other means;
(3) a reduction in the use of hazardous starting materials, reagents, or feedstocks;
(4) a reduction in potential toxicity, human exposure and/or environmental release; or
(5) the extent to which the new chemical substance may be a substitute for an existing substance that poses a greater overall risk to human health or the environment.

Information provided in this section will be taken into consideration during the review of this substance. See PMN Instructions Manual and Pollution Prevention Guidance manual for guidance and examples.

Enter Attachment filename for Pollution Prevention Page 11.	☐

PMN2010P12

SANITIZED SUBMISSION

PMN Page 12

Part III -- LIST OF ATTACHMENTS

Attach continuation sheets for sections of the form, test data and other data (including physical/chemical properties and structure/activity information), and optional information after this page. Clearly identify the attachment and the section of the form to which it relates, if appropriate. Number consecutively the pages of any paper attachments. In the Number of Pages column below, enter the inclusive page numbers of each attachment for paper submissions or enter the total number of pages for each attachment for electronic submissions. Electronic attachments can be identified by filename.
Mark (X) the "Confidential" box next to any attachment name or filename you claim as confidential. Read the Instructions Manual for guidance on how to claim any information in an attachment as confidential. You must include with the sanitized copy of the notice form a sanitized version of any attachment in which you claim information as confidential.

#	Attachment Name	Attachment Filename	Number of Pages	Associated PMN Section Number	CBI
001	CAS Inventory Expert Service Report		1	Pt.I, Sec.B, 1c.	
002	Continuation Sheet of PMN Page 4, Section B, Item 1.e.		1	Pt.I, Sec.B, 1e.	
003	Continuation Sheet of PMN Page 10, Section B, Item 1		1	Pt.2, Sec.B, 1a.	
004	Material Safety Data Sheet (#1)		7		
005	Material Safety Data Sheet (#2)		7		
006	Chromosomal Aberration Test ...		43		
007	Homogeneity, Stability And Concentration Analyses ...		15		
008	Mutagenicity Test ...		26		
009	Twenty-Eight-Day Repeated-Dose Oral Toxicity Study ...	-	216		

Mark (X) this box if the data continues on the next page. ☐

PMN2010P13

SANITIZED SUBMISSION

PMN Page 13

PHYSICAL AND CHEMICAL PROPERTIES WORKSHEET

The information on this page refers to chemical number(s): ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

To assist EPA's review of physical and chemical properties data, please complete the following worksheet for data you provide and include it in the notice. Identify the property measured, the value of the property, the units in which the property is measured (as necessary), and whether or not the property is claimed as confidential. Give the attachment number (found on page 12) in column (b). The physical state of the neat substance should be provided. These measured properties should be for the neat (100% pure) chemical substance. Properties that are measured for mixtures or formulations should be so noted (% PMN substance in __). You are not required to submit this worksheet; however, EPA strongly recommends that you do so, as it will simplify the review and ensure that confidential information is properly protected. You should submit this worksheet as a supplement to your submission of test data. This worksheet is not a substitute for submission of test data.

Property (a)		Unit	Mark X if Provided	Attachment Number (b)	Value (c) (solid)	Value (c) (liquid)	Value (c) (gas)	Measured or Estimate (M or E)	CBI Mark (X) (d)
Physical state of neat substance			☐		☐	☐	☐		X
Vapor Pressure @ Temperature		°C	☐				Torr		
Density/relative density			☐		XXX		g/cm3		X
Solubility									
@ Temperature	XXX	°C	☐		XXX		g/L		X
Solvent	XXX								
Solubility in Water @ Temperature		°C	☐				g/L		
Melting Temperature			☐				°C		
Boiling / Sublimation temperature @		Torr	☐				°C		
Spectra			☐						
Dissociation constant			☐						
Octanol / water partition coefficient			☐						
Henry's Law constant			☐						
Volatilization from water			☐						
Volatilization from soil			☐						
pH@ concentration	XXX		☐		XXX				X
Flammability			☐		XXX				X
Explodability			☐						
Adsorption / Coefficient			☐						
Particle Size Distribution			☐		XXX				X
Other – Specify			☐						

ATTACHMENT HEADER SHEET

Attachment Number 001

Attachment Name

CAS Inventory Expert Service Report

Associated PMN Section Number

Pt.I, Sec.B, 1c.

Does not contain CBI

Report Number

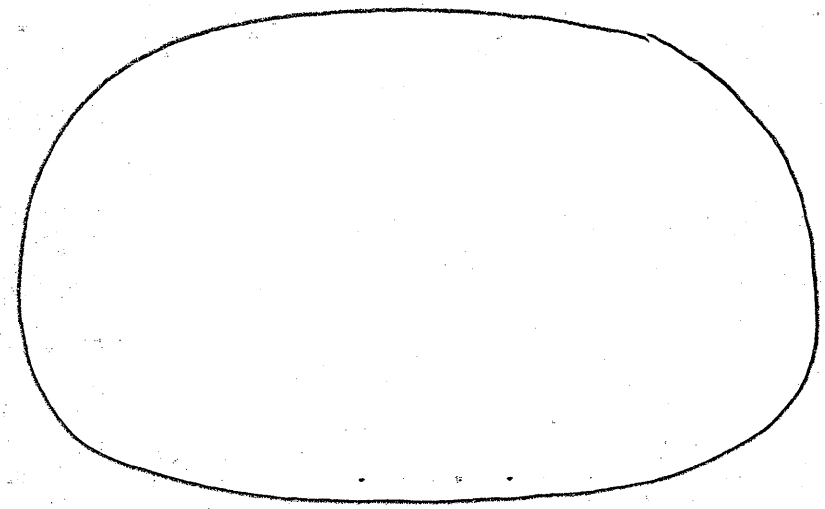
TSB2101224041049680

Inventory Expert Service

A division of the American Chemical Society

Phone: 800-631-1884, 614-447-3870
Fax: 614-447-3747
E-mail: answers@cas.org
Web: www.cas.org/products/client/

INVENTORY EXPERT SERVICE REPORT



Please print the above CA Index Name on the appropriate page of your PMN.

☐ **If this box is checked, CAS has made correction(s) marked in red to your IES order. Please make the same correction(s) to your PMN before submitting it to the EPA.**

CAS • 2540 Olentangy River Road • P.O. Box 3343 • Columbus, Ohio 43210-0334 • USA

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ATTACHMENT HEADER SHEET

Attachment Number 002

Attachment Name

Continuation Sheet of PMN Page 4, Section B, Item 1.e.

Associated PMN Section Number

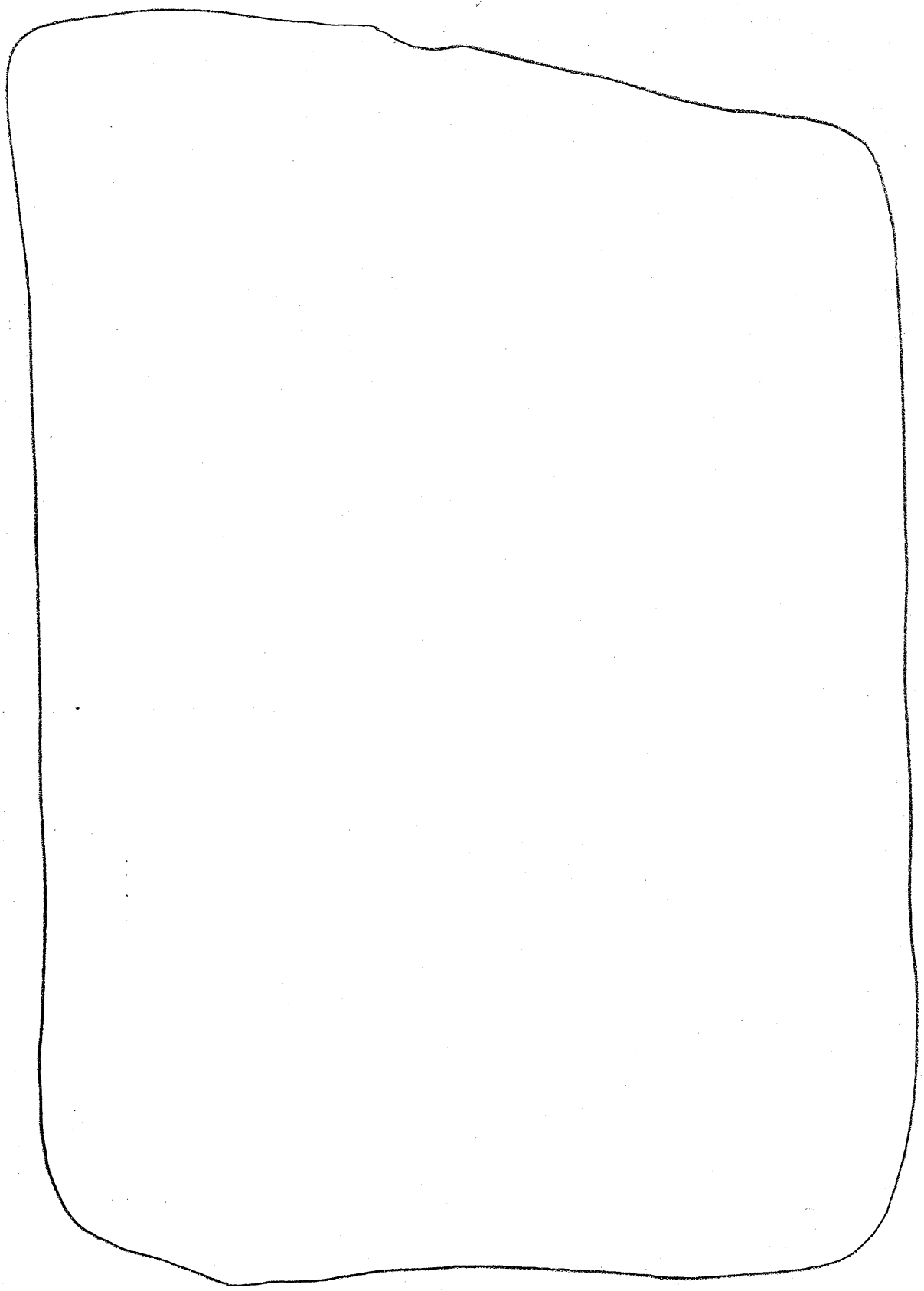
Pt.I, Sec.B, 1e.

Does not contain CBI

Report Number

TSB2101224041049680

Continuation Sheet of PMN Page 4, Section B, Item 1.e.



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ATTACHMENT HEADER SHEET

Attachment Number 003

Attachment Name

Continuation Sheet of PMN Page 10, Section B, Item 1

Associated PMN Section Number

Pt.2, Sec.B, 1a.

Does not contain CBI

Report Number

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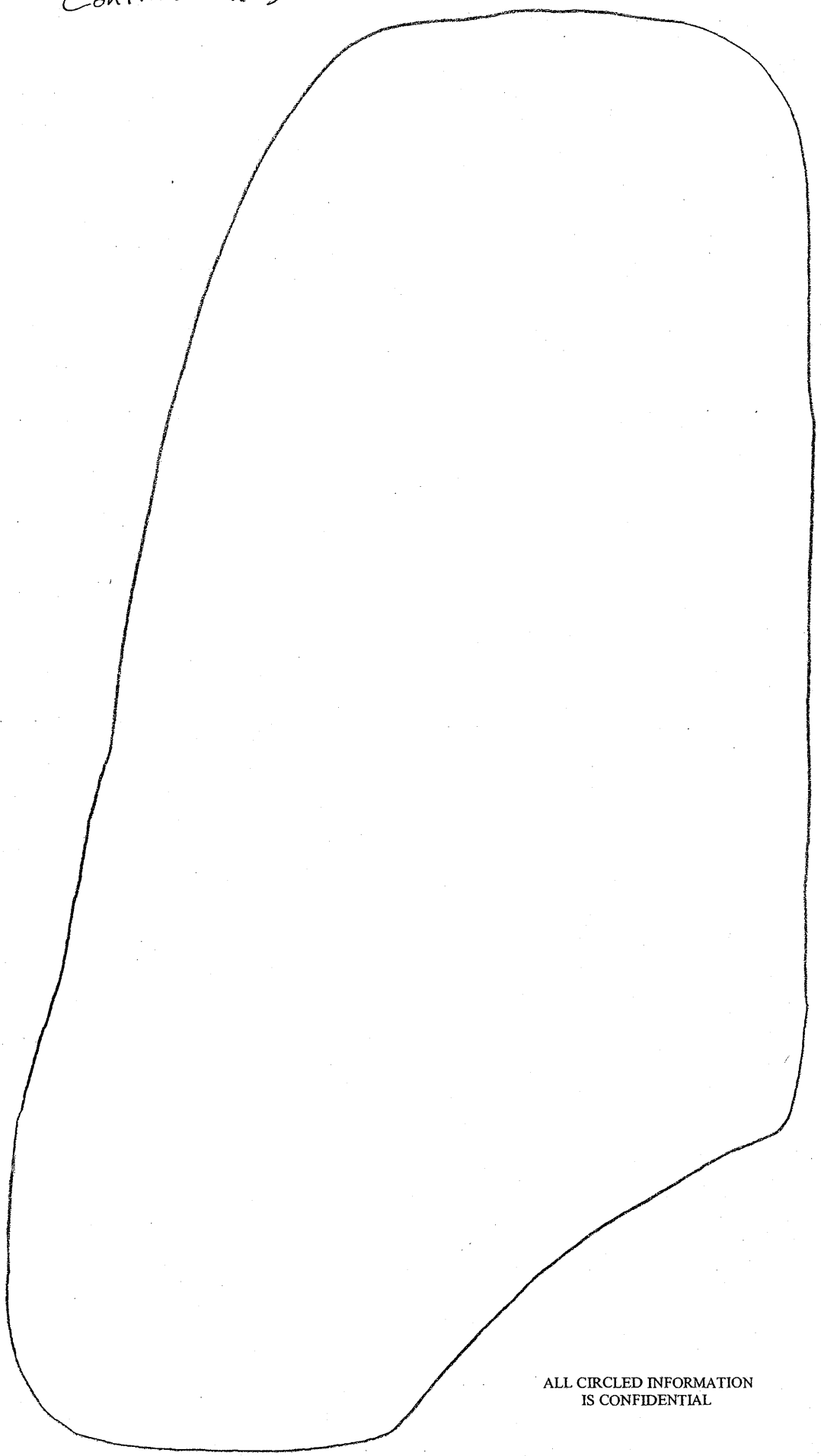
Continuation Sheet of PMN Page 10, Section B, Item 1



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ATTACHMENT HEADER SHEET

Attachment Number 004

Attachment Name

Material Safety Data Sheet (#1)

Associated PMN Section Number

N/A

Does not contain CBI

Report Number

TSB2101224041049680

MATERIAL SAFETY DATA SHEET (#1)

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

2. HAZARDS IDENTIFICATION

GHS Classification

		Lithium Titanate
Physical Hazards:		
	Explosives	Not applicable
	Flammable gases	Not applicable
	Flammable aerosols	Not applicable
	Oxidizing gases	Not applicable
	Gases under pressure	Not applicable
	Flammable liquids	Not applicable
	Flammable solids	Not classified
	Self-reactive substances and mixtures	Not applicable
	Pyrophoric liquids	Not applicable
	Pyrophoric solids	Not classified
	Self-heating substances and mixtures	Not classified
	Substances and mixtures which, in contact with water, emit flammable gases	Not classified
	Oxidizing liquids	Not applicable
	Oxidizing solids	Not classified
	Organic peroxides	Not applicable
	Corrosive to metals	Classification not possible

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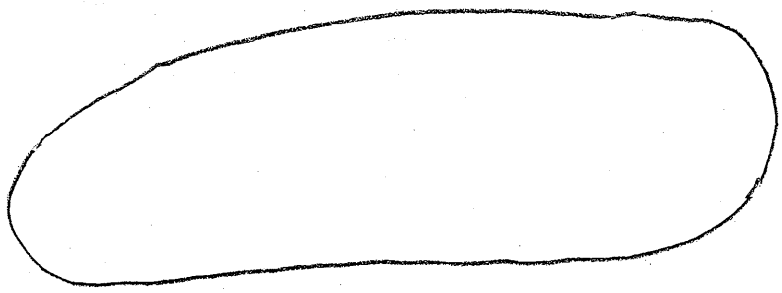

MATERIAL SAFETY DATA SHEET

Health Hazards:		
	Acute toxicity(oral)	Category 5
	Acute toxicity(dermal)	Classification not possible
	Acute toxicity(inhalation:gases)	Not applicable
	Acute toxicity(inhalation:vapor)	Classification not possible
	Acute toxicity(inhalation:dusts)	Classification not possible
	Acute toxicity(inhalation:mists)	Not applicable
	Skin corrosion/ irritation	Not classified
	Serious eye damage/ eye irritation	Classification not possible
	Respiratory sensitization	Classification not possible
	Skin sensitization	Classification not possible
	Germ cell mutagenicity	Classification not possible
	Carcinogenicity	Classification not possible
	Reproductive toxicity	Classification not possible
	Specific target organ toxicity -Single exposure	Classification not possible
	Specific target organ toxicity -Repeated exposure	Classification not possible
	Aspiration hazards	Classification not possible
Environmental Hazards:		
	Acute aquatic toxicity	Not classified
	Chronic aquatic toxicity	Category 4

GHS label elements, including precautionary statements.
Signal word: Warning
Pictograms or hazard symbols: None.

Hazard statements: May be harmful if swallowed.
May cause long lasting harmful effects to aquatic life.

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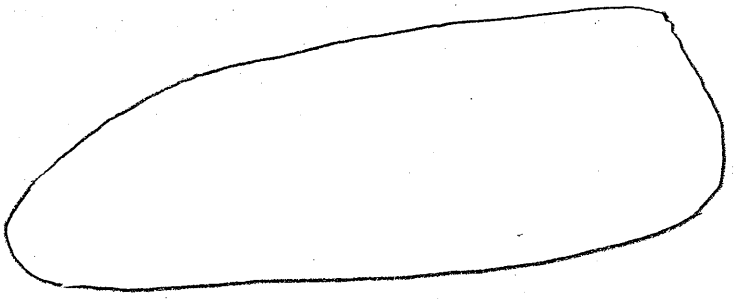


MATERIAL SAFETY DATA SHEET

Precautionary statements:

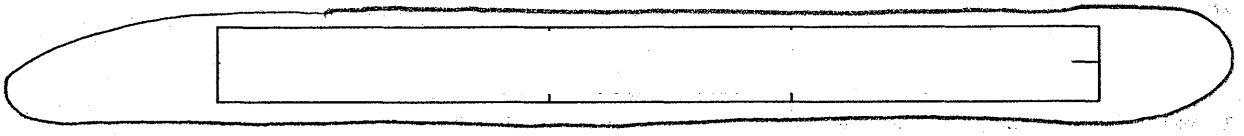
Do not eat, drink or smoke when using this product.
Use only outside or in a well-ventilated area.
Do not inhale dusts.
Wash hands at the end of work.
Avoid release to the environment.

Avoid storage at high-temperature and high-humidity.
Do not pile up high to prevent the second aggregation.
Do not store together with water.
Keep container tightly sealed.
Not regulated for packaging and container.

Get medical advice if you feel unwell.

Dispose in compliance with governmental and local regulations.

3. COMPOSITION, INFORMATION ON INGREDIENTS

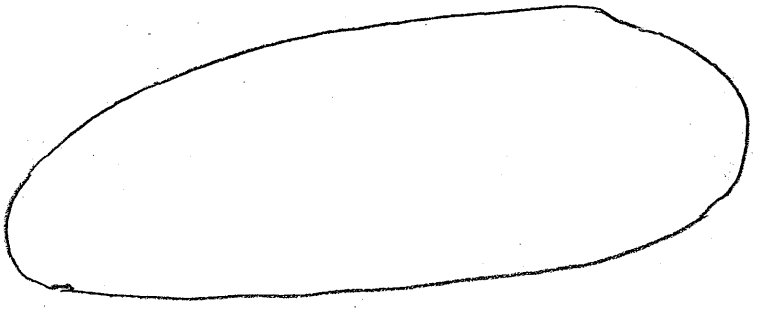


4. FIRST-AID MEASURES

Inhalation : Remove patient from exposure to fresh air, and call a physician.
Skin contact : Wash well with water and mild soap. If irritation is shown, call a physician.
Eye contact : Flush with plenty of water. Call a physician in case of necessity.
Ingestion : Rinse out the mouth, and call a physician.

5. FIRE-FIGHTING MEASURES

Incombustible
Extinguishing media : Not required. Use suitable extinguishing media for surrounding material and type of fire.
Special fire-fighting procedures : None.



MATERIAL SAFETY DATA SHEET

6. ACCIDENTAL RELEASE MEASURES

Personal precaution measures : None.

Environmental precautions and methods for clean up :

Prevent spilled material entering drains.

Waste material should be disposed of in accordance with governmental and local regulations.

7. HANDLING AND STORAGE

Handling : Keep work area free of spills.

Storage : Store in clean , dry place at room temperature.

8. EXPOSURE CONTROLS, PERSONAL PROTECTION

Control Parameters :

Not established

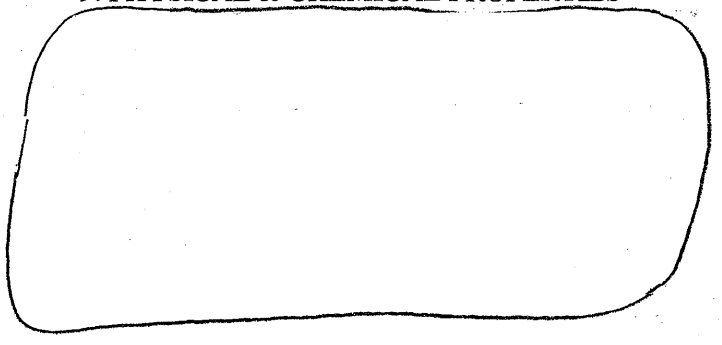
Personal protective equipment :

Respiratory : Use a Purifying respirator equipped with filter for protection against dust.

Eyes : Use safety glasses with side shields or goggles.

Skin : Use gloves and other protective clothing.

9. PHYSICAL & CHEMICAL PROPERTIES



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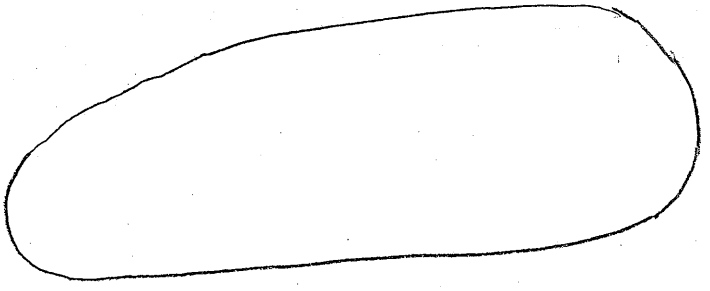


MATERIAL SAFETY DATA SHEET

10. STABILITY AND REACTIVITY

Stability :	Stable under normal conditions.
Conditions to avoid :	No data available.
Materials to avoid :	No data available.

11. TOXICOLOGICAL INFORMATION

Acute toxicity:

Oral: LD50＞2000mg/kg in female rats. (Category 5, AN-2966)

Skin corrosion/ irritation: No irritant in rabbits. (Not classified)
(company data AN-2978)

Serious eye damage and eye irritation:
No data available.

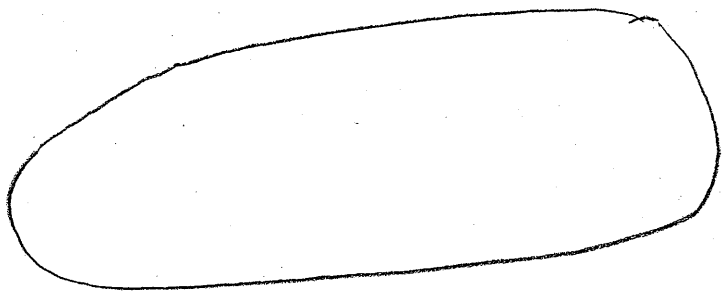
Germ cell mutagenicity: No data available in mutagenesis assay *in vivo* and in genotoxicity assay *in vivo*.
Negative by Ames test. (company data K01-4136)
D20=2.3mg/mL (Structural abnormality, Chromosomal aberration test *in vitro*) (company data K06-1270)
(Classification not possible)

Carcinogenicity: No data available.

Reproductive toxicity: No data available.

Specific target-organ toxicity-Single exposure:
No data available.

Specific target-organ toxicity-Repeated exposure:
No specific signs of toxicity were observed for 28-day oral administration test in rats (NOAEL=1000mg/kg). On the other hand, decrease of hemoglobin concentration and increase of reticulocyte-ratio in blood were observed at a dose of 1000mg/kg in female rats (NOEL=250mg/kg). (Classification not possible)
(company data B11-0897)



MATERIAL SAFETY DATA SHEET

Aspiration hazard: No data available.

12. ECOLOGICAL INFORMATION

Acute aquatic toxicity:

Fish(Oryzias latipes)	LC50>100mg/L(96hrs)
Crustacea(Daphnia magna)	LC50>100mg/L(48hrs)
Algal(unicellular green alga)	EbC50>100mf/L(72hrs)

Since it was suggested from the above (company data: ET2710, ET2810, ET2210) that the toxicity concerned is not shown in the water solubility (insoluble) of this material, it was considered as not classified.

Chronic aquatic toxicity : Although acute toxicity was not reported, it was a metallic compound, and since the underwater action was unknown, it was considered as category 4.

13. DISPOSAL CONSIDERATION

Comply with governmental and local regulations.

14. TRANSPORT INFORMATION

UN No.: Not applicable.
IMDG: Not regulated for transport.
Packing: Not dangerous for transport.

Not regulated for transport by DOT/ IMO/ IATA.

Do not pile up high to avoid falling and loosening. Product should be prevented from falling, loosening or tumbling during transport. Avoid direct sunlight.

15. REGULATORY INFORMATION

OSHA STATUS : None of the components in this material is defined as a hazardous substance.

TSCA STATUS : This material is not listed on TSCA inventory, however, each component such as [redacted] is listed on TSCA inventory.
All components are listed on TSCA inventory.

MATERIAL SAFETY DATA SHEET

SARA TITLE Ⅲ : This material does not contain toxic chemicals subject to the reporting requirements of section 313 of Title Ⅲ of the Superfund Amendments and Reauthorization Act of 1986 and 40 CFR Part 372.

HMIS Rating :

Health	1	Flammability	0
Reactivity	0	Personal Protection	F

16. OTHER INFORMATION

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ATTACHMENT HEADER SHEET

Attachment Number 005

Attachment Name

Material Safety Data Sheet (#2)

Associated PMN Section Number

N/A

Does not contain CBI

Report Number

TSB2101224041049680

MATERIAL SAFETY DATA SHEET (#2)

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

2. HAZARDS IDENTIFICATION

GHS Classification

		Lithium Titanate
Physical Hazards:		
	Explosives	Not applicable
	Flammable gases	Not applicable
	Flammable aerosols	Not applicable
	Oxidizing gases	Not applicable
	Gases under pressure	Not applicable
	Flammable liquids	Not applicable
	Flammable solids	Not classified
	Self-reactive substances and mixtures	Not applicable
	Pyrophoric liquids	Not applicable
	Pyrophoric solids	Not classified
	Self-heating substances and mixtures	Not classified
	Substances and mixtures which, in contact with water, emit flammable gases	Not classified
	Oxidizing liquids	Not applicable
	Oxidizing solids	Not classified
	Organic peroxides	Not applicable
	Corrosive to metals	Classification not possible

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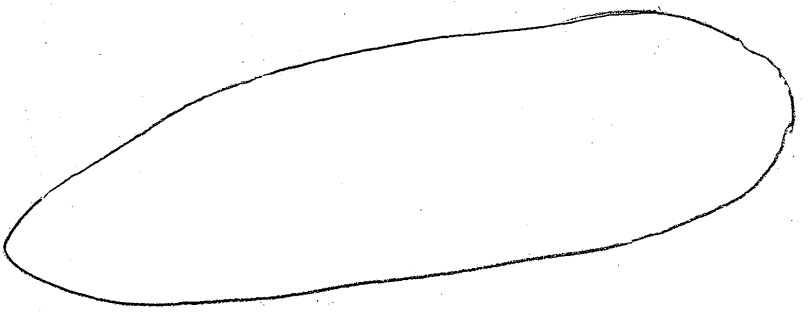

MATERIAL SAFETY DATA SHEET

Health Hazards:		
	Acute toxicity (oral)	Category 5
	Acute toxicity (dermal)	Classification not possible
	Acute toxicity (inhalation: gases)	Not applicable
	Acute toxicity (inhalation: vapor)	Classification not possible
	Acute toxicity (inhalation: dusts)	Classification not possible
	Acute toxicity (inhalation: mists)	Not applicable
	Skin corrosion/ irritation	Not classified
	Serious eye damage/ eye irritation	Classification not possible
	Respiratory sensitization	Classification not possible
	Skin sensitization	Classification not possible
	Germ cell mutagenicity	Classification not possible
	Carcinogenicity	Classification not possible
	Reproductive toxicity	Classification not possible
	Specific target organ toxicity -Single exposure	Classification not possible
	Specific target organ toxicity -Repeated exposure	Classification not possible
	Aspiration hazards	Classification not possible
Environmental Hazards:		
	Acute aquatic toxicity	Not classified
	Chronic aquatic toxicity	Category 4

GHS label elements, including precautionary statements.

Signal word: Warning

Pictograms or hazard symbols: None.

Hazard statements: May be harmful if swallowed.
May cause long lasting harmful effects to aquatic life.

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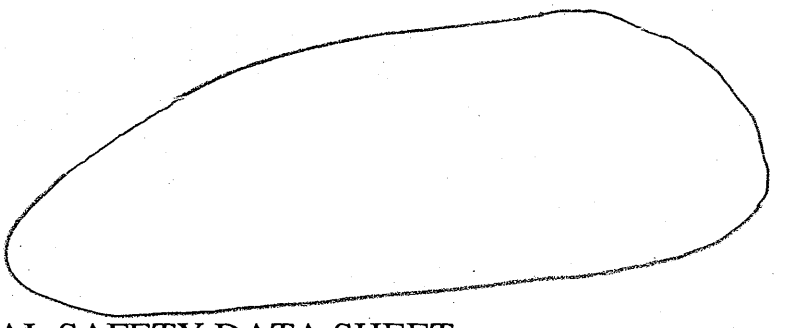
IS CONFIDENTIAL



MATERIAL SAFETY DATA SHEET

Precautionary statements:

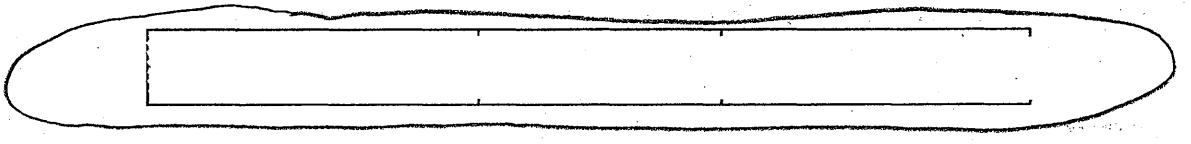
Do not eat, drink or smoke when using this product.
Use only outside or in a well-ventilated area.
Do not inhale dusts.
Wash hands at the end of work.
Avoid release to the environment.

Avoid storage at high-temperature and high-humidity.
Do not pile up high to prevent the second aggregation.
Do not store together with water.
Keep container tightly sealed.
Not regulated for packaging and container.

Get medical advice if you feel unwell.

Dispose in compliance with governmental and local regulations.

3. COMPOSITION, INFORMATION ON INGREDIENTS



4. FIRST-AID MEASURES

Inhalation : Remove patient from exposure to fresh air, and call a physician.
Skin contact : Wash well with water and mild soap. If irritation is shown, call a physician.
Eye contact : Flush with plenty of water. Call a physician in case of necessity.
Ingestion : Rinse out the mouth, and call a physician.

5. FIRE-FIGHTING MEASURES

Incombustible
Extinguishing media : Not required. Use suitable extinguishing media for surrounding material and type of fire.
Special fire-fighting procedures : None.

ALL CIRCLED INFORMATION IS CONFIDENTIAL

MATERIAL SAFETY DATA SHEET

6. ACCIDENTAL RELEASE MEASURES

Personal precaution measures : None.

Environmental precautions and methods for clean up :

Prevent spilled material entering drains.

Waste material should be disposed of in accordance with governmental and local regulations.

7. HANDLING AND STORAGE

Handling : Keep work area free of spills.

Storage : Store in clean , dry place at room temperature.

8. EXPOSURE CONTROLS, PERSONAL PROTECTION

Control Parameters :

Not established

Personal protective equipment :

Respiratory : Use a Purifying respirator equipped with filter for protection against dust.

Eyes : Use safety glasses with side shields or goggles.

Skin : Use gloves and other protective clothing.

9. PHYSICAL & CHEMICAL PROPERTIES

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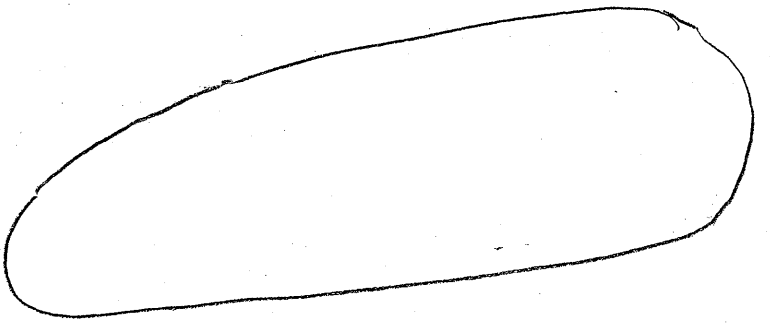


MATERIAL SAFETY DATA SHEET

10. STABILITY AND REACTIVITY

Stability :	Stable under normal conditions.
Conditions to avoid :	No data available.
Materials to avoid :	No data available.

11. TOXICOLOGICAL INFORMATION

Acute toxicity:

Oral: LD50＞2000mg/kg in female rats. (Category 5, AN-2966)

Skin corrosion/ irritation: No irritant in rabbits. (Not classified)
(company data AN-2978)

Serious eye damage and eye irritation:
No data available.

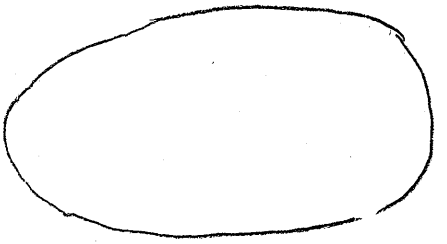
Germ cell mutagenicity: No data available in mutagenesis assay *in vivo* and in genotoxicity assay *in vivo*.
Negative by Ames test. (company data K01-4136)
D20=2.3mg/mL (Structural abnormality, Chromosomal aberration test *in vitro*) (company data K06-1270)
(Classification not possible)

Carcinogenicity: No data available.

Reproductive toxicity: No data available.

Specific target-organ toxicity-Single exposure:
No data available.

Specific target-organ toxicity-Repeated exposure:
No specific signs of toxicity were observed for 28-day oral administration test in rats (NOAEL=1000mg/kg). On the other hand, decrease of hemoglobin concentration and increase of reticulocyte-ratio in blood were observed at a dose of 1000mg/kg in female rats (NOEL=250mg/kg). (Classification not possible)
(company data B11-0897)



Aspiration hazard: No data available.

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12. ECOLOGICAL INFORMATION

Acute aquatic toxicity:

Fish(Oryzias latipes)	LC50>100mg/L(96hrs)
Crustacea(Daphnia magna)	LC50>100mg/L(48hrs)
Algal(unicellular green alga)	EbC50>100mf/L(72hrs)

Since it was suggested from the above (company data: ET2710, ET2810, ET2210) that the toxicity concerned is not shown in the water solubility (insoluble) of this material, it was considered as not classified.

Chronic aquatic toxicity : Although acute toxicity was not reported, it was a metallic compound, and since the underwater action was unknown, it was considered as category 4.

---

13. DISPOSAL CONSIDERATION

Comply with governmental and local regulations.

---

14. TRANSPORT INFORMATION

UN No.: Not applicable.
IMDG: Not regulated for transport.
Packing: Not dangerous for transport.

Not regulated for transport by DOT/ IMO/ IATA.

Do not pile up high to avoid falling and loosening. Product should be prevented from falling, loosening or tumbling during transport. Avoid direct sunlight.

---

15. REGULATORY INFORMATION

OSHA STATUS : None of the components in this material is defined as a hazardous substance.

TSCA STATUS : This material is not listed on TSCA inventory, however, each component such as _____ is listed on TSCA inventory.
All components are listed on TSCA inventory.

SARA TITLE Ⅲ : This material does not contain toxic chemicals subject to the reporting requirements of section 313 of Title Ⅲ of the Superfund Amendments and Reauthorization Act of 1986 and 40 CFR Part 372.

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MATERIAL SAFETY DATA SHEET

HMIS Rating :

Health	1	Flammability	0
Reactivity	0	Personal Protection	F

16. OTHER INFORMATION

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ATTACHMENT HEADER SHEET

Attachment Number 006

Attachment Name

Chromosomal Aberration Test ...

Associated PMN Section Number

N/A

Does not contain CBI

Report Number

TSB2101224041049680

CERI

Receipt No.837-08-T-5901

STUDY CODE: K06-1270

FINAL REPORT

CHROMOSOMAL ABERRATION TEST OF

USING CULTURED MAMMALIAN CELLS

March 2009

CERI Hita
Chemicals Evaluation and Research Institute, Japan

STATEMENT

TITLE OF STUDY

Chromosomal Aberration Test of [redacted] Using Cultured Mammalian Cells
(Study Code: K06-1270)

I, the undersigned, hereby declare that this report provides a correct English translation of the final report (Study Code: K06-1270, issued on March 26, 2009) audited by Quality Assurance Unit of CERI Hita, Chemicals Evaluation and Research Institute, Japan.

Saori Fujishima — October 16, 2009

Saori Fujishima
CERI Hita
Chemicals Evaluation and Research Institute, Japan

Date

ALL CIRCLED INFORMATION
IS CONFIDENTIAL

K06-1270

GLP STATEMENT

CERI Hita
Chemicals Evaluation and Research Institute, Japan

Title: Chromosomal Aberration Test of Using Cultured Mammalian Cells
Study Code: K06-1270

I, the undersigned, hereby declare that this study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Principles of Good Laboratory Practice" (November 26, 1997).

I also confirmed that this report accurately reflected the raw data and the test data were valid.

Study Director: Signed in original March 26, 2009
Shinya Wakamatsu

K06-1270
1/2

QUALITY ASSURANCE STATEMENT

CERI Hita
Chemicals Evaluation and Research Institute, Japan

Title: Chromosomal Aberration Test of Using Cultured Mammalian Cells
Study Code: K06-1270

This study was inspected by Quality Assurance Unit of CERI Hita, Chemicals Evaluation and Research Institute, Japan. The dates inspected and the dates reported these results to the study director and management are as follows.

Phase	Date of Inspection	Date Reported to Study Director and Management
Protocol	September 2, 2008	September 2, 2008
Preparation of Test Substance	September 4, 2008	September 4, 2008
Treatment of Cells	September 4, 2008	September 4, 2008
Confirmation of the Answer from Study Director (Protocol)	September 10, 2008	September 10, 2008
Protocol Amendment	September 16, 2008	September 16, 2008
Protocol Amendment (No. 2)	October 3, 2008	October 6, 2008
Observation of Specimens	November 5, 2008	November 5, 2008
Protocol Amendment (No. 3)	November 17, 2008	November 17, 2008
Confirmation of the Answer from Study Director (Protocol Amendment (No. 3))	November 21, 2008	November 21, 2008
Protocol Amendment (No. 4)	December 2, 2008	December 2, 2008
Raw Data and Draft Final Report	March 17, 2009	March 17, 2009
Reinspection of Raw Data and Draft Final Report	March 18, 2009	March 18, 2009
Draft Final Report (Second Time)	March 23, 2009	March 23, 2009
Reinspection of Draft Final Report (Second Time)	March 24, 2009	March 24, 2009
Final Report	March 26, 2009	March 26, 2009

The inspection result of following phase was reported to the study director and management based on the report of process-based inspection relevant to this study type and timeframe.

Phase	Date of Inspection	Date Reported to Study Director and Management
Examination of Solubility of the Test Substance	October 2, 2007	March 26, 2009
Preparation and Management of Positive Control Substance	May 23 and July 25, 2008	March 26, 2009
Preparation of Medium and Reagent	December 12, 2007	March 26, 2009
Management of Cells	November 30, 2007 and March 4, 2008	March 26, 2009
Cell Pre-culture	August 18, 2008	March 26, 2009
Collection of Cells and Preparation of Specimens	August 5 and 6, 2008	March 26, 2009

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study and that the reported results accurately reflect obtained raw data.

Head, Quality Assurance Unit: Signed in original March 26, 2009
Ryuichiro Mizuguchi

TABLE OF CONTENTS

Study Code: K06-1270
Test Substance Code: HR7578
Sponsor Code: I-0010

TITLE

Chromosomal Aberration Test of Using Cultured Mammalian Cells

SPONSOR

TESTING FACILITY

CERI Hita
Chemicals Evaluation and Research Institute, Japan
822, 3-chome, Ishii-machi, Hita, Oita 877-0061, Japan

PURPOSE OF STUDY

The ability of the test substance to induce chromosomal aberrations was examined by using Chinese hamster lung fibroblasts (CHL/IU cells).

TESTING METHOD

This study was conducted in accordance with "III Mutagenicity Test: Chromosomal Aberration Test Using Cultured Mammalian Cells" prescribed in "Concerning Testing Methods Relating to the New Chemical Substances" on Japanese Test Guideline (Notification No. 1121002 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 2 (November 13, 2003) of the Manufacturing Industries Bureau, METI & No. 031121002 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Guidelines for Testing of Chemicals, 473, *In Vitro* Mammalian Chromosome Aberration Test" (July 21, 1997).

GLP COMPLIANCE

This study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Principles of Good Laboratory Practice" (November 26, 1997).

PERIOD OF STUDY

Commencement of Study:	August 29, 2008
Initiation of Experiment (Initiation of Cell Growth Inhibition Test):	September 4, 2008
Completion of Experiment (Completion of Observation of Specimens):	January 9, 2009
Completion of Study:	March 26, 2009

STORAGE AND RETENTION PERIOD OF DATA

The raw data, protocol, protocol amendment, letter of test request, table of test substance information, final report, other record documents and specimens will be stored in the archive of this testing facility for 10 years after the date of receipt of the notification that they are applicable to Article 4, Paragraphs 1 or 2, Article 4-2, Paragraphs 2, 3 or 8, Article 5-4, Paragraph 2, Article 24, Paragraph 2 or Article 25-3, Paragraph 2 of the Japanese Chemical Substances Control Law No. 117 (1973). The sponsor will inform the date of receipt of the notification to the testing facility. After termination of the retention period, any measures taken will be done so with the approval of the sponsor.

The specimens to which the quality will be deteriorated will be retained only for the period when the quality can be secured. The sponsor's consent will be obtained before abandonment.

RETENTION OF ORIGINAL DOCUMENTS

An original protocol, original protocol amendments and an original final report will be retained at the testing facility. The copies of their original that the study director will be recognized to be accurate copy will be sent to the sponsor.

STUDY DIRECTOR AND PERSONS CONCERNED WITH THE STUDY AND THE OPERATION

Study Director: Shinya Wakamatsu
Section 3, CERI Hita

Persons Concerned with the Study and Their Operation:
Chisato Iwami
(Preparation of test substance formulation, cell treatment and microscopic observation of specimens)
Junko Kawaguchi
(Microscopic observation of specimens)

APPROVAL BY AUTHOR

Study Director: Signed in original March 26, 2009
Shinya Wakamatsu

SUMMARY

The ability of to induce chromosomal aberrations was investigated by using Chinese hamster lung fibroblasts (CHL/IU cells).

Based on the result of cell growth inhibition test, the doses in the chromosomal aberration test were set at 287, 574, 1150 and 2300 μg/mL in the short-term treatment without S9 mix, 1150, 2300 and 4590 μg/mL in the short-term treatment with S9 mix and 143, 287, 574 and 1150 μg/mL in the 24 hours continuous treatment.

In chromosomal aberration test, the observation doses for evaluation were selected at all four doses set in the short-term treatment without S9 mix, at all three doses set in the short-term treatment with S9 mix and at 143, 287 and 574 μg/mL in the 24 hours continuous treatment. Then, the frequencies of cells with structural aberrations and numerical aberration cells were examined.

As a result of observation of specimens, although the frequencies of cells with structural aberrations were below 5% at all doses of the test substance in the short-term treatment with S9 mix and the 24 hours continuous treatment, the maximum frequency of cells with structural aberrations was 5.5% in the short-term treatment without S9 mix and it was suspected to be positive. Then, the confirmation test for the short-term treatment without S9 mix was carried out. As a result, the maximum frequency of cells with structural aberrations was 6.5% and it was confirmed that there was reproducibility in the appearance of 5% or more structural aberration. Consequently, structural aberration was judged to be positive. On the other hand, the frequencies of numerical aberration cells were below 5% at all doses of the test substance in all treatment methods, therefore, numerical aberration was judged to be negative. The frequency of cells with structural aberrations was low because the maximum frequency was 6.5%, furthermore, D_{20} value was 2.3 mg/mL, which was more than 0.1 mg/mL. Therefore, it was considered that the ability of to induce chromosomal aberrations was weak.

The frequencies of cells with structural aberrations or numerical aberration cells in the negative control treated with distilled water were below 5%, and the frequencies of cells with structural aberrations in the positive controls treated with mitomycin C or cyclophosphamide monohydrate were above 20%, indicating the proper performance of the present study.

It was concluded that did not induce numerical aberration but slightly induced structural aberration under the present test conditions.

MATERIALS AND METHODS

1. TEST SUBSTANCE AND POSITIVE CONTROL SUBSTANCES

8) Storage conditions

Tightly sealed and stored at room temperature (cabinet No. 1 in the test substance storage room, permissible range: 10-30°C).

9) Precautions

Gloves, a mask, a head cap, safety glasses and a lab coat were worn.

1.2 Positive Control Substances

1) Mitomycin C (MMC)

Manufacturer:	Kyowa Hakko Kogyo Co., Ltd.
Lot No.:	513AGH
Appearance:	royal purple powder
Content:	102%
Grade:	for injection

2) Cyclophosphamide monohydrate (CPA)

Manufacturer:	Wako Pure Chemical Industries, Ltd.
Lot No.:	WKL2245
Appearance:	white crystals or crystalline powder
Content:	98.9%
Grade:	for biochemistry

3) Storage conditions

MMC was stored at room temperature (cabinet No. 2 in the test substance storage room, permissible range: 10-30°C) and CPA in a cold dark place (refrigerator No.005 in the test substance storage room, permissible range: 1-10°C).

4) Precautions

Gloves, a mask, a head cap and a lab coat were worn.

2. CELLS

2.1 Cell Line and Reason for Selection

Chinese hamster lung fibroblasts (CHL/IU cells) were supplied by Health Science Research Resources Bank, Japan Health Sciences Foundation on April 17, 2002. The modal number of chromosomes was 25 per cell. The doubling time was about 15 hours. It was confirmed in the testing facility that the cells were mycoplasma free and the spontaneous frequencies of cells with structural aberrations and the numerical aberration cells were below 5%.

CHL/IU cells have been recommended the availability on *in vitro* chromosome aberration test prescribed in "Concerning Testing Methods Relating to the New Chemical Substances" on Japanese Test Guideline and "OECD Guidelines for Testing of Chemicals, 473, *In Vitro* Mammalian Chromosome Aberration Test".

2.2 Storage

Cells were suspended in medium [Eagle's minimum essential medium (Nissui

Pharmaceutical Co., Ltd.) and 10 vol% heat-inactivated newborn calf serum (NBCS, Sanko Junyaku Co., Ltd.)] including 10 vol% DMSO and were frozen in liquid nitrogen.

2.3 Culture Condition

Cells were cultured in a CO_2 incubator (MCO-18AIC, SANYO Electric Co.), which was set at 37°C and 5% CO_2 under humid condition.

2.4 Subculture

Cells were subcultured in 90-mm diameter Petri dishes (Nunc A/S) twice a week. Passage number of cells was at 7 for the cell growth inhibition test, 13 for the chromosomal aberration test and 10 for the confirmation test after the receipt.

3. MEDIUM AND S9 MIX

3.1 Medium

L-Glutamine (final concentration: 0.292 g/L) and sodium hydrogen carbonate (final concentration: approximately 1.85 g/L) were added to Eagle's minimum essential medium (Lot No. 588803, Nissui Pharmaceutical Co., Ltd.) and basal medium (MEM) was prepared. This medium was then supplemented with 10 vol% heat-inactivated NBCS (Lot No. ASC29136, HyClone).

3.2 S9 Mix

1) Rat liver S9

S9 (Lot No. 08051602, manufactured on May 16, 2008, S9 protein content: 22.2 mg/mL, Oriental Yeast Co., Ltd.), which was prepared from livers of 7-week-old male SD rats (body weight: 210.3±8.2 g) administered intraperitoneally a combination of phenobarbital (one time at 30 mg/kg and three times at 60 mg/kg) and 5,6-benzoflavone (one time at 80 mg/kg) was used. S9 was frozen and preserved in an ultra-deep freezer (MDF-U481ATR, SANYO Electric Co., Ltd., the tolerance temperature: below -80°C) until use. S9 was used within six months after the day of manufacturing.

2) Composition of S9 mix

One milliliter of S9 mix consisted of 0.3 mL S9, 5 μmol $MgCl_2$, 33 μmol KCl, 5 μmol G-6-P, 4 μmol NADP and 4 μmol HEPES (pH 7.2) and S9 mix was prepared just prior to use and was stored in ice until use.

4. CELL PRE-CULTURE

A 60-mm diameter plastic dish (Asahi Glass Co., Ltd.) was used for cell culture. Five milliliter of a cell suspension of 5.0×10^3 cells/mL were seeded into a dish and were cultured continuously for 3 days.

5. PREPARATION OF TEST SUBSTANCE FORMULATION AND POSITIVE CONTROL SUBSTANCE SOLUTIONS

5.1 Preparation of Test Substance Formulation

1) Solvent

Distilled water (Lot No. K8A90, for injection, Otsuka Pharmaceutical Factory Inc.)

2) Reason for selection of solvent

The test substance was homogenously suspended in distilled water (459 mg/mL) and DMSO (459 mg/mL) and not become homogenous suspension at 45.9 mg/mL in acetone. The test substance formulation at 459 mg/mL in distilled water was not indicated any change in color nor exothermic at room temperature within 2 hours after preparation. Therefore, distilled water was selected as a solvent in this study.

3) Preparation method

After the test substance was weighed, distilled water was added to the test substance to make an original formulation using a laboratory mixer. The test substance formulations of 100 times concentrations of the test substance in the medium were prepared with the solvent. It was prepared without correcting purity of the test substance because the purity of the test substance was above 95%.

4) Preparation time

The test substance formulations were prepared immediately before use, stored at room temperature and used within 1 hour after preparation.

5.2 Preparation of Positive Control Substance Solutions

1) Preparation method and storage

MMC and CPA were dissolved in distilled water at 0.01 mg/mL and 1 mg/mL, respectively. The positive control substance solutions were frozen in an ultra-deep freezer (MDF-U481ATR, SANYO Electric Co., Ltd., the tolerance temperature: below -80°C).

2) Preparation time and expiry in use

The positive control substance solutions were thawed at the time of use and used within 1.5 hours. The stock solutions were used within 6 months after preparation.

6. TEST PROCEDURE

6.1 Cell Growth Inhibition Test

1) Procedure

For the short-term treatment without S9 mix, the medium was removed from a pre-culture, and the cells were treated for 6 hours in well-mixed medium containing 30 μL of the test substance formulation or the solvent and 3 mL of the fresh medium. For the short-term treatment with S9 mix, the medium was removed from a pre-culture, and the cells were treated for 6 hours in well-mixed medium consisting of

0.5 mL of S9 mix and 30 μL of the test substance formulation or the solvent and 2.5 mL of the fresh medium. After treatment, the medium was removed, and the cells were rinsed 3 times with 2 mL of Dulbecco's physiological phosphate buffered solution without Ca^{2+} and Mg^{2+}. Cells were then cultured for another 18 hours in 5 mL of fresh medium.

For the continuous treatment, the medium was removed from a pre-culture, and the cells were treated for 24 hours with well-mixed medium containing 50 μL of the test substance formulation or the solvent and 5 mL of the fresh medium.

In the short-term and the continuous treatments, 50 μL of a 10 μg/mL demecolcine solution was added to each dish at 2 hours before the end of the culture.

At the start and the end of the treatment and at the end of the culture, precipitation of the test substance, the color change of the medium and the corrosion of the dish were observed macroscopically.

At the end of the culture, a cell suspension was prepared to collect from each dish by a treatment with 2 mL of 0.25 w/v% trypsin. After 200 μL of the cell suspension was diluted with 10 mL of Cell Pack (Sysmex Corporation), the number of the cells was measured using a Microcell counter (CDA-500, Sysmex Corporation), and the cell growth rate and the 50% cell growth inhibition concentration (IC_{50}) was calculated. The IC_{50} was obtained from a linear line drawn between 2 plots; the one being greater and the other lower than, and both closest to 50% of the cell growth rate.

Remained cells were collected by a centrifugation at 1000 rpm (185×g) for 5 minutes and were treated hypotonically with 3 mL of 0.075 mol/L KCl at 37°C for 15 minutes. Following the hypotonic treatment, the cells were pre-fixed once with approximately 0.3 mL of a fixative solution (methanol : acetic acid = 3 : 1), and were completely fixed twice with 3 mL of fixative solution. Then, the cell suspension was prepared with a fixative solution, two drops of the suspension were placed on a glass slide, and stained about 15 minutes with 2 vol% Giemsa solution in 1/15 mol/L phosphate buffer solution (pH6.8). One specimen was prepared per dose.

2) Dose levels

In each treatment method, the highest dose was set at 4590 μg/mL equivalent to 10 mmol/L, as the maximum dose in the case of no cytotoxicity on the guideline, and 17.9, 35.9, 71.7, 143, 287, 574, 1150 and 2300 μg/mL were set based on a geometric progression of 2, respectively. Duplicate dishes were used for each dose.

3) Observation and scoring

Specimens were observed to check the presence or absence of mitotic metaphase cells, and the frequency of the cells with chromosomal aberrations was calculated by

observed 50 metaphase cells per dose at which the dose setting of chromosomal aberration test was considered to be referred.

(1) Structural aberration

The number of cells with structural aberrations excluding gaps was recorded. Gaps were defined as an achromatic region smaller than the width of one chromatid.

(2) Numerical aberration

The number of cells showing triploid or more was scored.

6.2 Chromosomal Aberration Test

1) Procedure

Chromosomal aberration test was carried out using the same procedure as that of the cell growth inhibition test, with the following positive controls. Four specimens per dose (two specimens per dish) were prepared.

Treatment method		Substance	Dose
Short-term treatment	Without S9 mix	MMC	0.1 μg/mL
	With S9 mix	CPA	6 μg/mL
24 hours continuous treatment		MMC	0.05 μg/mL

In the positive control, each dish was added with 30 μL of a 0.01 mg/mL MMC solution and 18 μL of a 1 mg/mL CPA solution for the short-term treatments without and with S9 mix, respectively, and 25 μL of a 0.01 mg/mL MMC solution for the continuous treatment.

2) Dose levels of the test substance

The dose levels of the test substance were set on the basis of results of the cell growth inhibition test. The setting doses and the reason for selection are shown below.

In the short-term treatment with S9 mix, because a cytotoxicity that the cell growth rate was below 50% was not obtained, the highest dose was selected at 4590 μg/mL equivalent to 10 mmol/L and the following three doses were set based on a geometric progression of 2. In the short-term treatment without S9 mix and the continuous treatment, because a cytotoxicity that the cell growth rate was below 50% was obtained, the highest dose was selected at the dose that was over IC_{50}. Therefore, the highest dose was selected at 2300 μg/mL in the short-term treatment without S9 mix and 1150 μg/mL in the continuous treatment, and the following four doses were set based on a geometric progression of 2.

Treatment method		Setting doses of test substance
Short-term treatment	Without S9 mix	287, 574, 1150 and 2300 μg/mL
	With S9 mix	1150, 2300 and 4590 μg/mL
24 hours continuous treatment		143, 287, 574 and 1150 μg/mL

Duplicate dishes were used for each dose.

3) Observation

(1) Dose for observation

All specimens of the negative and the positive controls set as the control groups were observed. The observation doses of the test substance were selected the consecutive doses of three stages. The observation doses and the reason for selection are shown below.

In the short-term treatment with S9 mix, because a cytotoxicity that the cell growth rate was below 50% was not obtained, the observation doses of the test substance were selected at all setting doses. In the short-term treatment without S9 mix and the continuous treatment, because a cytotoxicity that the cell growth rate was below 50% was obtained, the highest dose for observation was selected at the lowest dose that the cell growth rate was below 50%. The lowest dose that the cell growth rate was below 50% was at 2300 μg/mL in the short-term treatment without S9 mix and 574 μg/mL in the continuous treatment, and it was considered that chromosomal aberrations were observable at these doses, therefore, the highest dose for observation were selected at those doses, and the following three consecutive doses were set.

Treatment method		Observation doses of test substance
Short-term treatment	Without S9 mix	574, 1150 and 2300 μg/mL
	With S9 mix	1150, 2300 and 4590 μg/mL
24 hours continuous treatment		143, 287 and 574 μg/mL

After the selection of the observation doses, randomly slide numbers were allocated to all observed specimens. All specimens were observed in a blinded manner.

As a result of the observation of specimens, the frequency of the cells with structural aberrations was over 5% at 574 μg/mL in the short-term treatment without S9 mix. Therefore, in the short-term treatment without S9 mix, the additional observation of specimens at 287 μg/mL was conducted in order to evaluate the no-observed effect level that the frequency of aberrant cells become below 5%. The slide numbers were allocated to all specimens to be observed additionally.

(2) Structural Aberration

Two hundred metaphase cells per dose (50 cells per specimen) containing 25±2 chromosomes were observed using a microscope. The total number of cells with structural aberrations and the number of aberrant cells and the number of aberrations in each aberration category were recorded. Gaps were defined as an achromatic region smaller than the width of one chromatid and were recorded separately from the structural aberrations.

(3) Numerical Aberration

The number of polyploid (cell with 38 or more chromosomes) cells among 200 metaphase cells per dose (50 cells per specimen) observed was recorded.

6.3 Confirmation Test

In the chromosomal aberration test, it was suspected to be positive, because cells with structural aberrations was observed more than 5% but less than 10% in the short-term treatment without S9 mix. Therefore, the confirmation test for the short-term treatment without S9 mix was carried out to confirm reproducibility of increase in the frequencies of cells with structural aberrations. The highest dose was selected at 2300 μg/mL and a total of five doses, 143, 287, 574 and 1150 μg/mL based on a geometric progression of 2, was set in the confirmation test.

In the confirmation test, because the lowest dose that the cell growth rate was below 50% was 574 μg/mL, the doses for observation were selected at 143, 287 and 574 μg/mL. The test procedures in the confirmation test were carried out in accordance with the chromosomal aberration test.

7. JUDGEMENT CRITERIA OF RESULTS

The findings were judged to be positive when the frequencies of cells with structural aberrations or numerical aberrations were 10% or more with a dose-related increase, or the frequencies of aberrant cells were 5% or more both in the chromosomal aberration test and the confirmation test. The other cases were judged to be negative. D_{20} value indicating a concentration that chromosomal aberration was observed in 20% of cells was calculated in the treatment method that the frequencies of cells with chromosomal aberrations were 5% or more.

8. VALIDITY OF TEST

This study was regarded as valid as follows: 1) the frequencies of cells with chromosomal aberrations did not fluctuate markedly between two culture dishes, 2) the frequencies of aberrant cells in the negative control were below 5%, and 3) the frequencies of cells with structural aberrations in the positive controls were 20% or more.

FACTORS AFFECTED RELIABILITY OF TEST

There were no factors, which might affect the reliability of the test.

TEST RESULTS

1. CELL GROWTH INHIBITION TEST (Table 1 and Fig. 1)

The IC_{50} were calculated at 910 μg/mL in the short-term treatment without S9 mix, more than 4590 μg/mL in the short-term treatment with S9 mix and at 330 μg/mL in the 24 hours continuous treatment.

In all treatment methods, precipitation of the test substance was observed at all doses of the test substance at the start of the treatment, at 35.9 μg/mL or more at the end of the treatment. At the end of the culture, precipitation of the test substance was observed at 35.9 μg/mL or more in the short-term treatment without S9 mix, at 574 μg/mL or more in the short-term treatment with S9 mix.

The frequencies of cells with structural aberrations were below 5% at all observation doses of the test substance in the short-term treatment with S9 mix and the 24 hours continuous treatment. However, the maximum frequency of cells with structural aberrations was 6.0% in the short-term treatment without S9 mix and the increase of the structural aberration was observed. The frequencies of numerical aberration cells were below 5% at all observation doses of the test substance in each treatment.

2. CHROMOSOMAL ABERRATION TEST

2.1 Short-term Treatment (Tables 2, 3 and Figs. 2, 3)

1) Without S9 mix

(1) Cell growth rate and IC_{50}

The cell growth rates at 287, 574, 1150 and 2300 μg/mL of the test substance were 76.7, 57.6, 50.7 and 38.0%, respectively. The IC_{50} was calculated at 1200 μg/mL.

(2) Precipitation of the test substance, color change of medium and corrosion of culture dish

Precipitation of the test substance was observed at all doses of the test substance at the start and the end of the treatment and the end of the culture. The color change of the medium and the corrosion of the culture dish were not observed at any doses.

(3) Frequency of cells with structural aberrations

The frequencies of cells with structural aberrations were 2.0% in the negative control and 66.5% in the positive control.

The frequencies of cells with structural aberrations at 287, 574, 1150 and 2300 μg/mL of the test substance were 1.0, 5.5, 2.0 and 5.0%, respectively, and were more than 5% but less than 10%, therefore, the induction of aberration was suspected.

(4) Frequency of numerical aberration cells

The frequencies of numerical aberration cells were below 5% at all doses including

the negative and positive controls, therefore, the results were judged to be negative.

(5) D_{20} value

It was calculated at 3.1 mg/mL for structural aberration.

2) With S9 mix

(1) Cell growth rate and IC_{50}

The cell growth rates at 1150, 2300 and 4590 μg/mL of the test substance were 81.8, 68.3 and 57.7%, respectively. The IC_{50} was calculated more than 4590 μg/mL.

(2) Precipitation of the test substance, color change of medium and corrosion of culture dish

Precipitation of the test substance was observed at all doses of the test substance at the start and the end of the treatment and the end of the culture. The color change of the medium and the corrosion of the culture dish were not observed at any doses.

(3) Frequency of cells with structural aberrations

The frequencies of cells with structural aberrations were 1.0% in the negative control and 38.0% in the positive control.

The frequencies of cells with structural aberrations at 1150, 2300 and 4590 μg/mL of the test substance were 1.0, 2.0 and 2.0%, respectively, and were below 5%, therefore, the results were judged to be negative.

(4) Frequency of numerical aberration cells

The frequencies of numerical aberration cells were below 5% at all doses including the negative and positive controls, therefore, the results were judged to be negative.

2.2 Twenty Four Hours Continuous Treatment (Tables 2, 4 and Figs. 2, 4)

1) Cell growth rate and IC_{50}

The cell growth rates at 143, 287, 574 and 1150 μg/mL of the test substance were 75.8, 61.9, 42.9 and 26.6%, respectively. The IC_{50} was calculated at 470 μg/mL.

2) Precipitation of the test substance, color change of medium and corrosion of culture dish

Precipitation of the test substance was observed at all doses of the test substance at the start and the end of the treatment. The color change of the medium and the corrosion of the culture dish were not observed at any doses.

3) Frequency of cells with structural aberrations

The frequencies of cells with structural aberrations were 0.5% in the negative control and 71.0% in the positive control.

The frequencies of cells with structural aberrations at 143, 287 and 574 μg/mL were 1.5, 2.0 and 3.0%, respectively, and were below 5%, therefore, the results were judged to be negative.

4) Frequency of numerical aberration cells

The frequencies of numerical aberration cells were below 5% at all doses including

the negative and positive controls, therefore, the results were judged to be negative.

3. CONFIRMATION TEST IN SHORT-TERM TREATMENT WITHOUT S9 MIX (TABLES 5, 6 AND FIGS. 5, 6)

3.1 Cell Growth Rate and IC_{50}

The cell growth rates at 143, 287, 574, 1150 and 2300 μg/mL of the test substance were 90.0, 70.1, 48.6, 29.5 and 17.8%, respectively. The IC_{50} was calculated at 560 μg/mL.

3.2 Precipitation of the Test Substance, Color of Medium and Corrosion of Culture Dish

Precipitation of the test substance was observed at all doses of the test substance at the start and the end of the treatment and the end of the culture. The color change of the medium and the corrosion of the culture dish were not observed at any doses.

3.3 Frequency of Cells with Structural Aberrations

The frequencies of cells with structural aberrations were 2.5% in the negative control and 64.5% in the positive control.

The frequencies at 143, 287 and 574 μg/mL were 1.0, 3.5 and 6.5%, respectively. Therefore, it was confirmed that there was the reproducibility in the appearance of the cells with structural aberration at a frequency of more than 5%.

3.4 Frequency of Numerical Aberration Cells

The frequencies of numerical aberration cells were below 5.0% at all doses including the negative and positive controls, therefore, the results were judged to be negative.

3.5 D_{20} Value

It was calculated at 2.3 mg/mL for structural aberration.

4. TYPICAL PHOTOS

The normal cell was shown in photo 1 and cells with structural aberration induced by)were shown in photos 2 and 3.

5. RESULTS OF OBSERVATION OF CHROMOSOMES IN ACCORDANCE WITH "CONCERNING TESTING METHODS RELATING TO THE NEW CHEMICAL SUBSTANCES" ON JAPANESE TEST GUIDELINE AND BACKGROUND DATA

The results of observation of chromosomes in accordance with "Concerning Testing Methods Relating to the New Chemical Substances" on Japanese Test Guideline were attached to APPENDIX 1. The number of aberrations was shown in Table 3, 4 and 6 and the number of cells with aberration was shown in APPENDIX 1. Background data of the negative and the positive controls in the testing facility were attached to APPENDIX 2.

DISCUSSION AND CONCLUSION

In each treatment method in the chromosomal aberration test, the frequencies of cells with chromosomal aberrations did not fluctuate markedly between two culture dishes, and the frequencies of cells with aberrations were below 5% in the negative controls, and the frequencies of cells with structural aberrations excluding gaps were 20% or more in the positive controls, indicating that the present study was appropriately performed.

As a result of the chromosomal aberration test, although the frequencies of cells with structural aberrations were below 5% at all doses of the test substance in the short-term treatment with S9 mix and the 24 hours continuous treatment, the maximum frequency of cells with structural aberrations was 5.5% in the short-term treatment without S9 mix and it was suspected to be positive. Therefore, the confirmation test for the short-term treatment without S9 mix was carried out. As a result, the maximum frequency of cells with structural aberrations was 6.5% and it was confirmed that there was the reproducibility in the appearance of the cells with structural aberrations at a frequency of more than 5%. Consequently, structural aberration was judged to be positive. On the other hand, the frequencies of numerical aberration cells were below 5% at all doses of the test substance in all treatment methods, therefore, numerical aberration was judged to be negative. However, the frequency of cells with structural aberrations was low because the maximum frequency was 6.5%, furthermore, D_{20} value was 2.3 mg/mL, which was more than 0.1 mg/mL. Therefore, it was considered that the ability of [redacted] to induce chromosomal aberrations was weak.

Based on the above results, it was concluded that [redacted] did not induce numerical aberration but slightly induced structural aberration under the present test conditions.

REFERENCES

1. Toshio Sofuni (ed.) (1999) Data book of chromosomal aberration test *in vitro*. Revised edition, 1998 (in Japanese). Life-science Information Center.
2. Japan Environmental Mutagenicity Society/Mammalian Mutagenicity Study Group (ed.) (1988) Atlas of chromosomal aberration induced with chemical substance (in Japanese). Asakura Publishing Co., Tokyo.

Table 1 Results of cell growth inhibition test of

Substance	Dose (μg/mL)	Treatment-recovery time (hour)	S9 mix	Cell growth rate (%)	Precipitation of test substance in medium [a]			Index of metaphase cells	Frequency of cells with aberrations (%)[b]	
					Treatment start	Treatment end	Culture end		Structural aberration	Numerical aberration
D.W.	0	6-18	-	100	-	-	-	abundant	4.0	0.0
	17.9	6-18	-	105.6	+	-	-	abundant	n.o.	n.o.
	35.9	6-18	-	105.8	+	+	+	abundant	n.o.	n.o.
	71.7	6-18	-	95.8	+	+	+	abundant	n.o.	n.o.
	143	6-18	-	100.0	+	+	+	abundant	n.o.	n.o.
	287	6-18	-	90.5	+	+	+	abundant	n.o.	n.o.
	574	6-18	-	62.6	+	+	+	abundant	n.o.	n.o.
	1150	6-18	-	41.2	+	+	+	abundant	4.0	2.0
	2300	6-18	-	25.8	+	+	+	abundant	4.0	0.0
	4590	6-18	-	19.6	+	+	+	abundant	6.0	4.0
				IC_{50}: 910 μg/mL						
D.W.	0	6-18	+	100	-	-	-	abundant	0.0	0.0
	17.9	6-18	+	106.9	+	-	-	abundant	n.o.	n.o.
	35.9	6-18	+	100.5	+	+	-	abundant	n.o.	n.o.
	71.7	6-18	+	105.1	+	+	-	abundant	n.o.	n.o.
	143	6-18	+	98.8	+	+	-	abundant	n.o.	n.o.
	287	6-18	+	110.1	+	+	-	abundant	n.o.	n.o.
	574	6-18	+	97.1	+	+	+	abundant	n.o.	n.o.
	1150	6-18	+	100.0	+	+	+	abundant	2.0	0.0
	2300	6-18	+	82.3	+	+	+	abundant	4.0	4.0
	4590	6-18	+	59.6	+	+	+	abundant	2.0	0.0
				IC_{50}: >4590 μg/mL						
D.W.	0	24-0	-	100	-	-		abundant	0.0	0.0
	17.9	24-0	-	96.1	+	-		abundant	n.o.	n.o.
	35.9	24-0	-	87.2	+	+		abundant	n.o.	n.o.
	71.7	24-0	-	87.4	+	+		abundant	n.o.	n.o.
	143	24-0	-	70.8	+	+		abundant	n.o.	n.o.
	287	24-0	-	52.4	+	+		abundant	2.0	0.0
	574	24-0	-	35.9	+	+		abundant	2.0	0.0
	1150	24-0	-	17.2	+	+		abundant	0.0	4.0
	2300	24-0	-	8.8	+	+		few meta	n.o.[c]	n.o.[c]
	4590	24-0	-	7.8	+	+		few meta	n.o.[c]	n.o.[c]
				IC_{50}: 330 μg/mL						

D.W.: Distilled water

n.o.: not observed, abundant: metaphases existed abundantly,

few meta: the frequency of metaphases was extremely few.

a) Precipitation of the test substance: -, absence; +, presence.

b) The frequency of cells with chromosomal aberrations was calculated by observing 50 metaphases per dose.

c) Because precipitation of the test substance was found on specimens, it was difficult to observe the aberration of chromosomes.

The highest dose was set at 4590 μg/mL equivalent to 10 mmol/L, as the maximum dose in case of no cytotoxicity on the guidelines, the dose levels based on a geometric progression of 2 were selected.

K06-1270

Table 2 Results of chromosomal aberration test of

Substance	Dose (μg/mL)	Treatment-recovery time (hour)	S9 mix	Cell growth rate (%)	Precipitation of test substance in medium [a]			Index of metaphase cells	Frequency of cells with aberrations (%)[b]	
					Treatment start	Treatment end	Culture end		Structural aberration	Numerical aberration
D.W.	0	6-18	-	100	-	-	-	abundant	2.0	0.0
	287	6-18	-	76.7	+	+	+	abundant	1.0	1.5
	574	6-18	-	57.6	+	+	+	abundant	5.5	0.0
	1150	6-18	-	50.7	+	+	+	abundant	2.0	2.5
	2300	6-18	-	38.0	+	+	+	abundant	5.0	0.5
MMC	0.1	6-18	-	ND	-	-	-	n.o.	66.5	0.0
			IC_{50} : 1200 μg/mL					D_{20} : 3.1 mg/mL		-
D.W.	0	6-18	+	100	-	-	-	abundant	1.0	0.5
	1150	6-18	+	81.8	+	+	+	abundant	1.0	1.0
	2300	6-18	+	68.3	+	+	+	abundant	2.0	0.5
	4590	6-18	+	57.7	+	+	+	abundant	2.0	0.0
CPA	6	6-18	+	ND	-	-	-	n.o.	38.0	0.0
			IC_{50} : >4590 μg/mL							
D.W.	0	24-0	-	100	-	-		abundant	0.5	0.5
	143	24-0	-	75.8	+	+		abundant	1.5	0.5
	287	24-0	-	61.9	+	+		abundant	2.0	1.0
	574	24-0	-	42.9	+	+		abundant	3.0	0.5
	1150	24-0	-	26.6	+	+		abundant	n.o.[c]	n.o.[c]
MMC	0.05	24-0	-	ND	-	-		n.o.	71.0	0.5
			IC_{50} : 460 μg/mL							

D.W.: Distilled water

MMC: mitomycin C, CPA: cyclophosphamide monohydrate

ND: not detected, n.o.: not observed, abundant: metaphases existed abundantly.

a) Precipitation of the test substance: -, absence; +, presence.

b) The frequency of cells with chromosomal aberrations was calculated by observing 200 metaphases per dose.

c) Because precipitation of the test substance was found on specimens, it was difficult to observe the aberration of chromosomes.

Table 3 Results of chromosomal aberration test (short-term treatments)

Name of test substance

K06-1270

Treatment time (h)	S9 mix	Dose (μg/mL)	Number of structural chromosomal aberrations (Average)						Total number of cells with structural aberrations (frequency%)	Number of gaps (frequency%)	Cell growth rate (%)	Number of cells with numerical chromosomal aberrations (frequency%)			
			Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others				Number of cells observed	Polyploids	Others	Total number of cells with aberrations
6 - 18	-	Negative control (D.W.) 0	100	2	1	0	0	0	3	1	100	100	0	0	0
			100	1	0	0	0	0	1	0		100	0	0	0
			200	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	1 (0.5)		200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	-	287 †	100	0	0	0	0	0	0	0	79.7	100	2	0	2
			100	2	1	0	0	0	2	1	73.7	100	1	0	1
			200	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.5)	(76.7)	200	3 (1.5)	0 (0.0)	3 (1.5)
6 - 18	-	574 †	100	1	3	0	0	0	4	0	55.7	100	0	0	0
			100	5	2	0	0	0	7	2	59.5	100	0	0	0
			200	6 (3.0)	5 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	11 (5.5)	2 (1.0)	(57.6)	200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	-	1150 †	100	0	0	0	0	0	0	0	55.1	100	4	0	4
			100	2	2	0	0	0	4	0	46.2	100	1	0	1
			200	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(50.7)	200	5 (2.5)	0 (0.0)	5 (2.5)
6 - 18	-	2300 †	100	3	1	0	0	0	4	0	37.3	100	0	0	0
			100	5	2	0	0	0	6	0	38.6	100	1	0	1
			200	8 (4.0)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	10 (5.0)	0 (0.0)	(38.0)	200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	-	Positive control (MMC) 0.1	100	56	102	0	0	0	68	3		100	0	0	0
			100	68	74	1	0	0	65	4		100	0	0	0
			200	124 (62.0)	176 (88.0)	1 (0.5)	0 (0.0)	0 (0.0)	133 (66.5)	7 (3.5)		200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	+	Negative control (D.W.) 0	100	0	0	0	0	0	0	0	100	100	1	0	1
			100	1	0	0	1	0	2	0		100	0	0	0
			200	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)		200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	+	1150 †	100	2	2	0	0	0	1	0	80.3	100	2	0	2
			100	1	0	0	0	0	1	1	83.2	100	0	0	0
			200	3 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.5)	(81.8)	200	2 (1.0)	0 (0.0)	2 (1.0)
6 - 18	+	2300 †	100	2	1	0	0	0	3	0	70.6	100	1	0	1
			100	0	1	0	0	0	1	0	65.9	100	0	0	0
			200	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(68.3)	200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	+	4590 †	100	2	1	0	0	0	3	0	62.4	100	0	0	0
			100	0	1	0	0	0	1	0	52.9	100	0	0	0
			200	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(57.7)	200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	+	Positive control (CPA) 6	100	16	34	0	0	0	34	0		100	0	0	0
			100	15	35	1	0	0	42	1		100	0	0	0
			200	31 (15.5)	69 (34.5)	1 (0.5)	0 (0.0)	0 (0.0)	76 (38.0)	1 (0.5)		200	0 (0.0)	0 (0.0)	0 (0.0)

Treatment time comprised treatment-time and recovery-time.

The number of aberrantions or aberrant cells at each dish was shown at the first and second lines. The total number of them was show at the third line.

Cell growth rate at each dish was shown at the first and second lines. The average of them was shown at the third line.

D.W.: Distilled water

MMC: Mitomycin C

CPA: Cyclophosphamide monohydrate

†: Precipitation of the test substance was observed at the start and the end of the treatment and the end of the culture.

Table 4 Results of chromosomal aberration test (continuous treatment)

Name of test substance :

K06-1270

Treatment time (h)	Dose (μg/mL)	Number of structural chromosomal aberrations (Average)						Total number of cells with structural aberrations (frequency%)	Number of gaps (frequency%)	Cell growth rate (%)	Number of cells with numerical chromosomal aberrations (frequency%)			
		Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others				Number of cells observed	Polyploids	Others	Total number of cells with aberrations
24 - 0	Negative control (D.W.)	100	0	0	0	0	0	0	0	100	100	1	0	1
		100	0	0	0	1	0	1	2		100	0	0	0
	0	200	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	2 (1.0)		200	1 (0.5)	0 (0.0)	1 (0.5)
24 - 0	143 †	100	4	0	0	0	0	3	0	77.2	100	1	0	1
		100	0	0	0	0	0	0	0	74.4	100	0	0	0
		200	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	(75.8)	200	1 (0.5)	0 (0.0)	1 (0.5)
24 - 0	287 †	100	2	0	0	0	0	2	0	59.0	100	1	0	1
		100	1	1	0	0	0	2	0	64.8	100	1	0	1
		200	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(61.9)	200	2 (1.0)	0 (0.0)	2 (1.0)
24 - 0	574 †	100	2	2	0	0	0	3	0	37.7	100	0	0	0
		100	3	1	0	0	0	3	0	48.1	100	1	0	1
		200	5 (2.5)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.0)	0 (0.0)	(42.9)	200	1 (0.5)	0 (0.0)	1 (0.5)
24 - 0	Positive control (MMC)	100	48	99	0	1	0	72	2		100	1	0	1
		100	74	94	0	0	0	70	1		100	0	0	0
	0.05	200	122 (61.0)	193 (96.5)	0 (0.0)	1 (0.5)	0 (0.0)	142 (71.0)	3 (1.5)		200	1 (0.5)	0 (0.0)	1 (0.5)

Treatment time comprised treatment-time and recovery-time.

The number of aberrantions or aberrant cells at each dish was shown at the first and second lines. The total number of them was show at the third line.

Cell growth rate at each dish was shown at the first and second lines. The average of them was shown at the third line.

D.W.: Distilled water

MMC: Mitomycin C

†: Precipitation of the test substance was observed at the start and the end of the treatment.

K06-1270

Table 5 Results of confirmation test of

Substance	Dose (μg/mL)	Treatment-recovery time (hour)	S9 mix	Cell growth rate (%)	Precipitation of test substance in medium [a]			Index of metaphase cells	Frequency of cells with aberrations (%)[b]	
					Treatment start	Treatment end	Culture end		Structural aberration	Numerical aberration
D.W.	0	6-18	-	100	-	-	-	abundant	2.5	2.0
	143	6-18	-	90.0	+	+	+	abundant	1.0	2.0
	287	6-18	-	70.1	+	+	+	abundant	3.5	3.0
	574	6-18	-	48.6	+	+	+	abundant	6.5	0.5
	1150	6-18	-	29.5	+	+	+	abundant	n.o.	n.o.
	2300	6-18	-	17.8	+	+	+	abundant	n.o.	n.o.
MMC	0.1	6-18	-	ND	-	-	-	n.o.	64.5	0.5
			IC_{50} :	560 μg/mL					D_{20} : 2.3 mg/mL	-

D.W.: Distilled water

MMC: mitomycin C

ND: not detected, n.o.: not observed, abundant: metaphases existed abundantly.

a) Precipitation of the test substance: -, absence; +, presence.

b) The frequency of cells with chromosomal aberrations was calculated by observing 200 metaphases per dose.

Table 6 Results of confirmation test (short-term treatment without S9 mix)

Name of test substance:

K06-1270

Treatment time (h)	S9 mix	Dose (μg/mL)	Number of structural chromosomal aberrations (Average)						Total number of cells with structural aberrations (frequency%)	Number of gaps (frequency%)	Cell growth rate (%)	Number of cells with numerical chromosomal aberrations (frequency%)			
			Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others				Number of cells observed	Polyploids	Others	Total number of cells with aberrations
6 - 18	-	Negative control (D.W.)	100	0	2	0	0	0	2	1	100	100	1	0	1
			100	3	0	0	0	0	3	0		100	3	0	3
		0	200	3 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.5)	1 (0.5)		200	4 (2.0)	0 (0.0)	4 (2.0)
6 - 18	-	143 †	100	0	2	0	0	0	2	0	91.4	100	3	0	3
			100	0	0	0	0	0	0	0	88.5	100	1	0	1
			200	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	(90.0)	200	4 (2.0)	0 (0.0)	4 (2.0)
6 - 18	-	287 †	100	4	1	0	0	0	5	0	70.3	100	4	0	4
			100	0	2	0	0	0	2	0	69.9	100	2	0	2
			200	4 (2.0)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	7 (3.5)	0 (0.0)	(70.1)	200	6 (3.0)	0 (0.0)	6 (3.0)
6 - 18	-	574 †	100	7	0	0	0	0	7	0	46.6	100	1	0	1
			100	5	1	0	0	0	6	0	50.5	100	0	0	0
			200	12 (6.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	13 (6.5)	0 (0.0)	(48.6)	200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	-	Positive control (MMC)	100	52	91	0	0	0	66	2		100	0	0	0
			100	38	81	0	0	1	63	2		100	1	0	1
		0.1	200	90 (45.0)	172 (86.0)	0 (0.0)	0 (0.0)	1 (0.5)	129 (64.5)	4 (2.0)		200	1 (0.5)	0 (0.0)	1 (0.5)

Treatment time comprised treatment-time and recovery-time.

The number of aberrantions or aberrant cells at each dish was shown at the first and second lines. The total number of them was show at the third line.

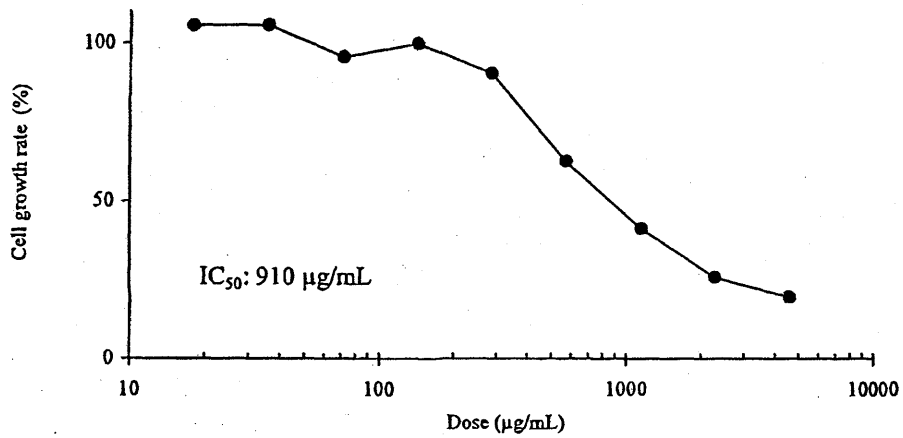
Cell growth rate at each dish was shown at the first and second lines. The average of them was shown at the third line.

Multiple that the number of aberration in the same aberration category appeared 10 or more was shown at others in structural chromosomal aberrations.

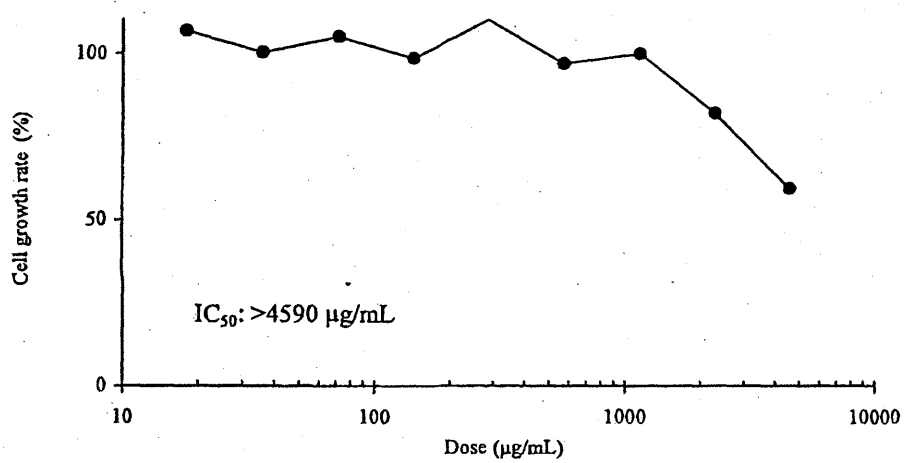
D.W.: Distilled water

MMC: Mitomycin C

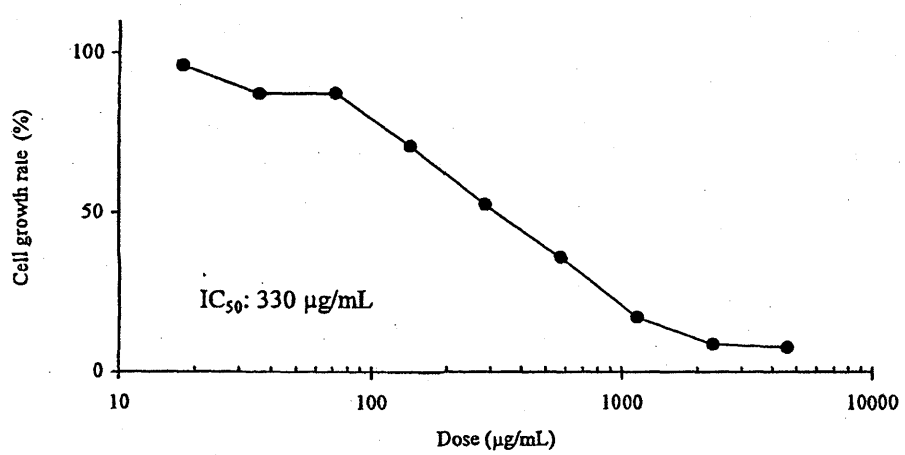
†: Precipitation of the test substance was observed at the start and the end of the treatment and the end of the culture.



Short-term treatment without S9 mix

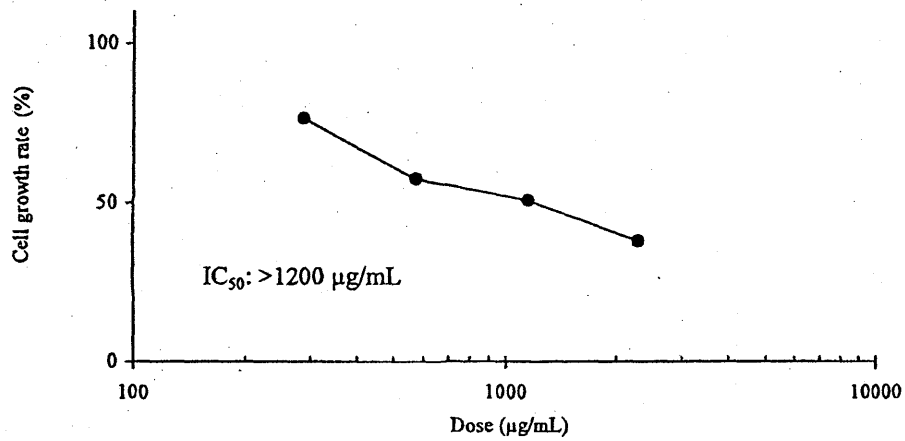


Short-term treatment with S9 mix

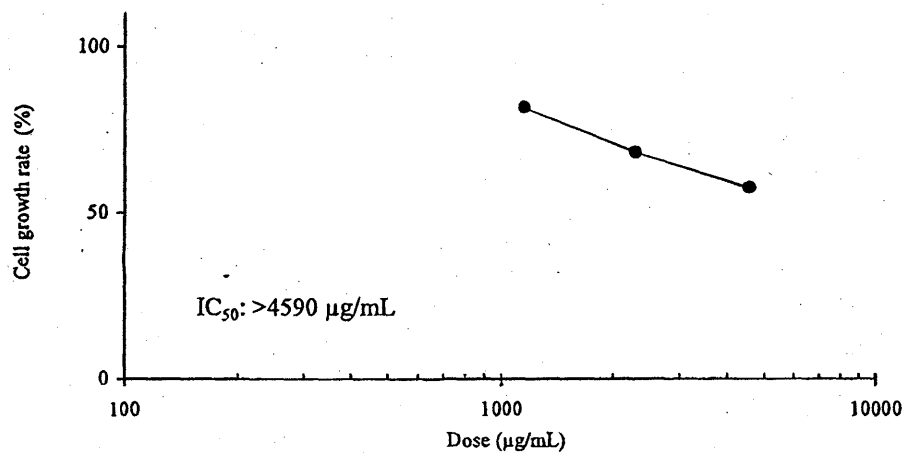


24 hours continuous treatment

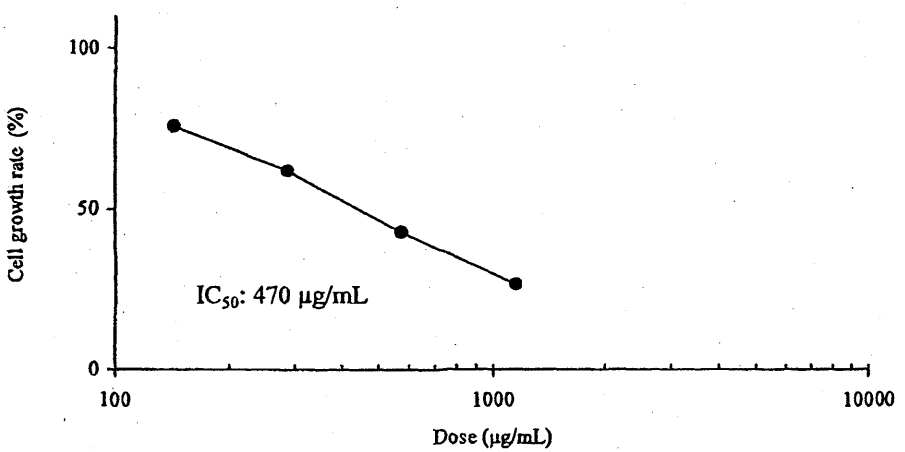
Fig. 1 Results of cell growth inhibition test of



Short-term treatment without S9 mix

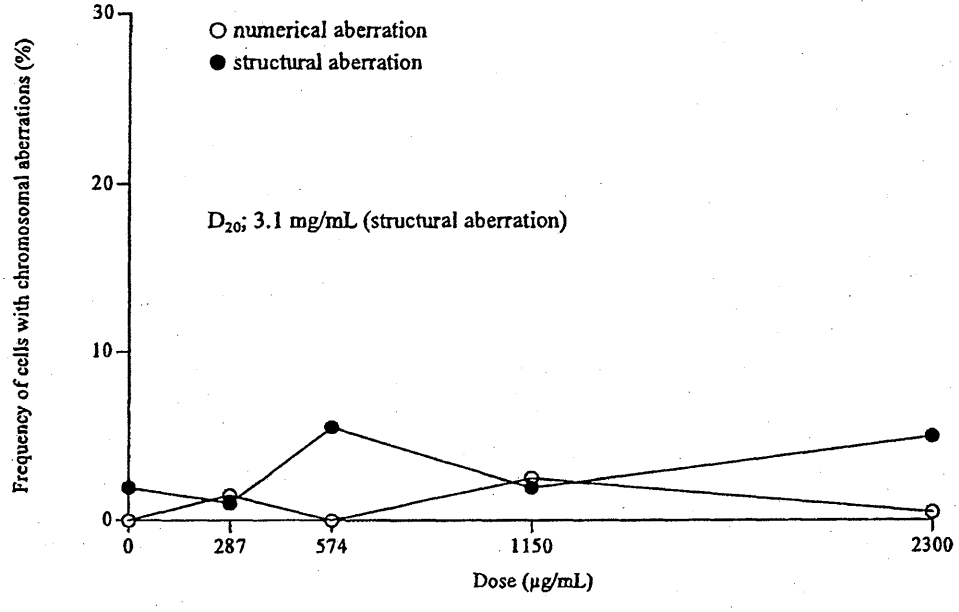


Short-term treatment with S9 mix

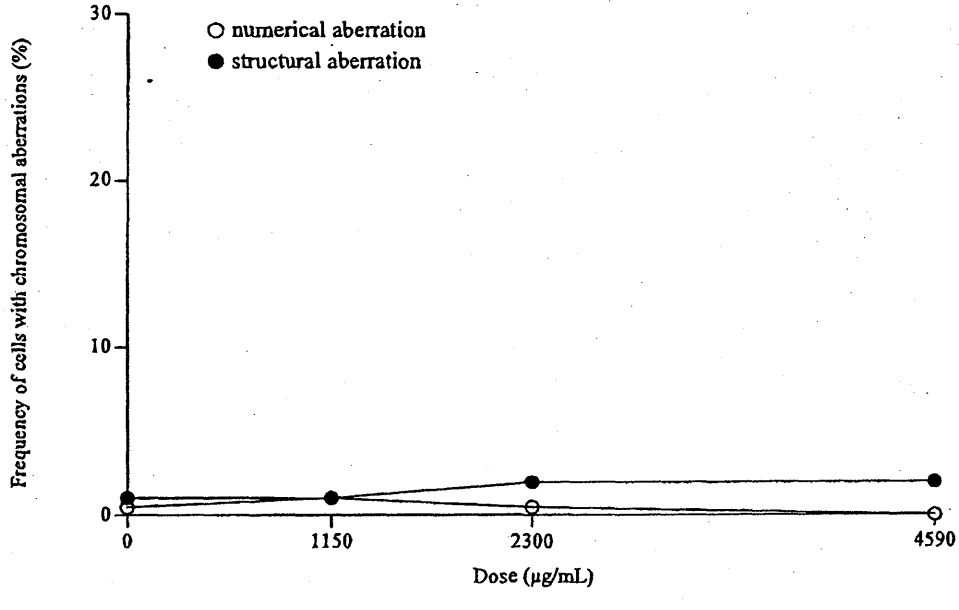


24 hours continuous treatment

Fig. 2 Cell growth rate in chromosomal aberration test of;



Without S9 mix



With S9 mix

Fig. 3 Results of chromosomal aberration test in short-term treatments of

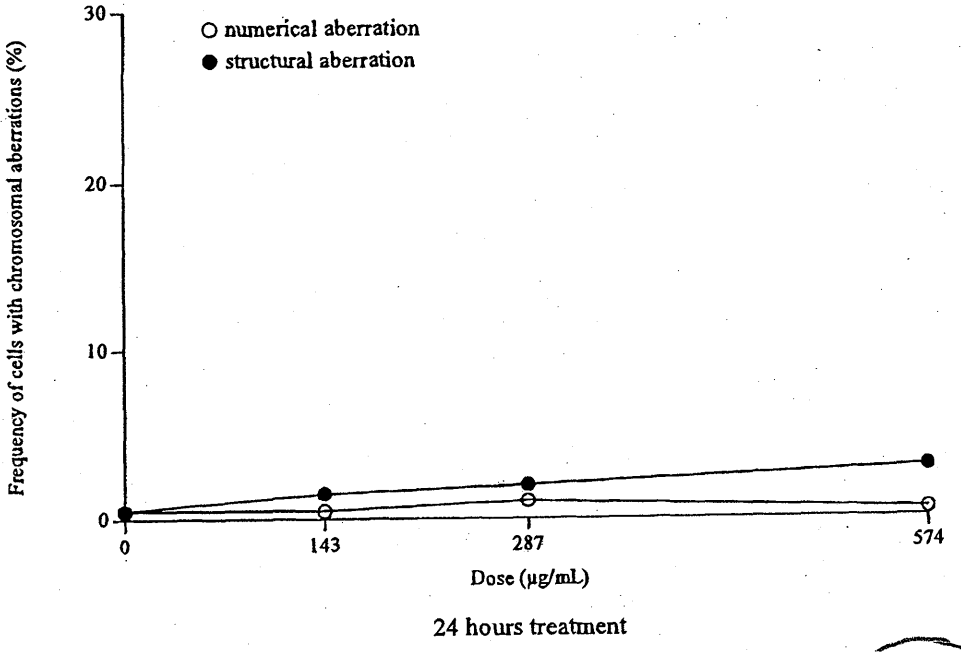
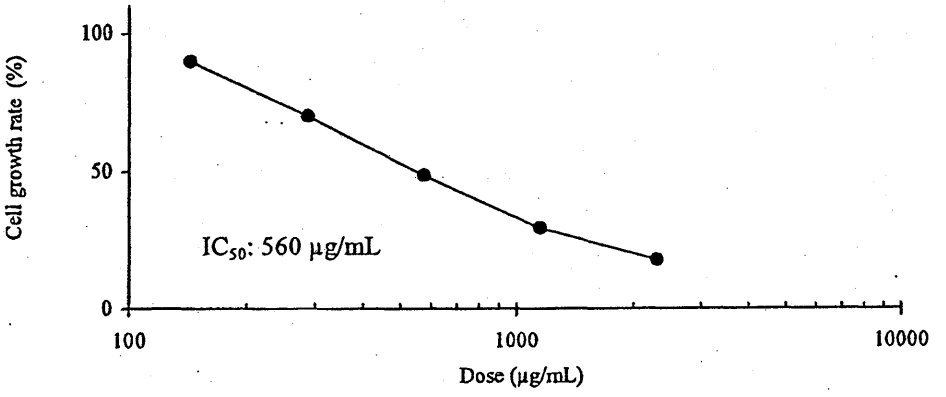
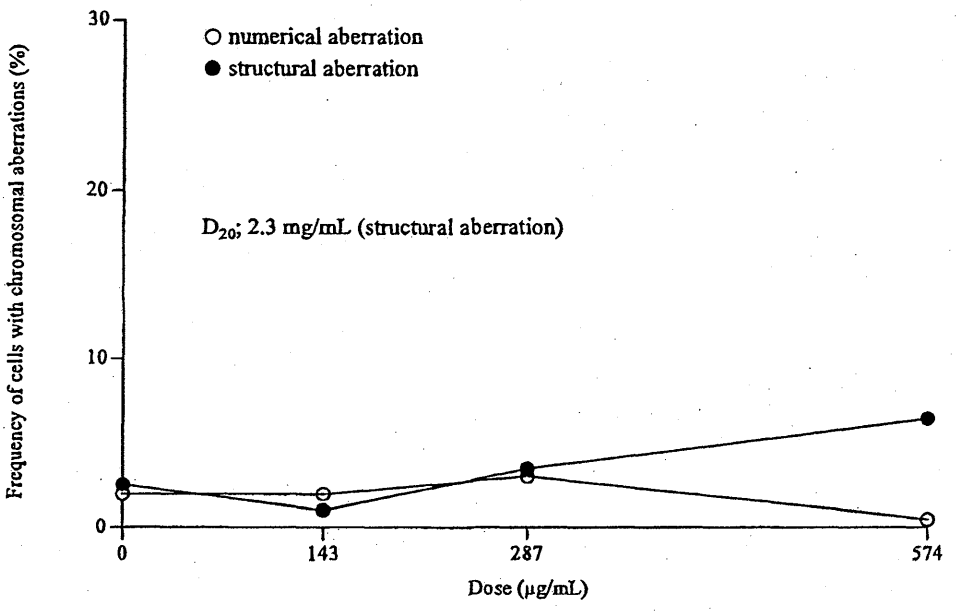


Fig. 4 Results of chromosomal aberration test in continuous treatment of



Short-term treatment without S9 mix

Fig. 5 Cell growth rate in confirmation test of



Without S9 mix

Fig. 6 Results of confirmation test in short-term treatment of

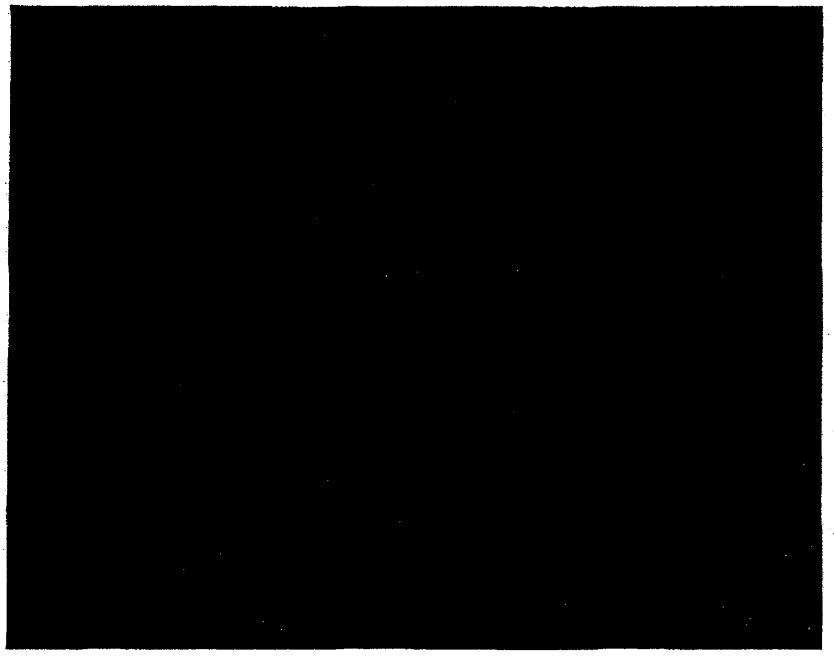


Photo 1 Normal cell

Negative control for short-term treatment with S9 mix in chromosomal aberration test

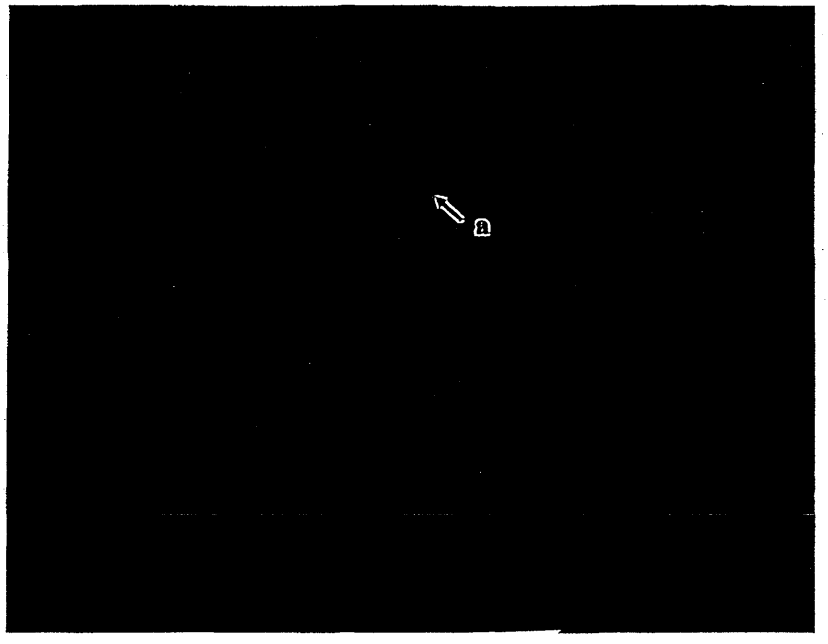


Photo 2 Structural aberration induced by

574 μg/mL for short-term treatment without S9 mix in chromosomal aberration test

a: chromatid break (precipitation of the test substance was found on specimens)

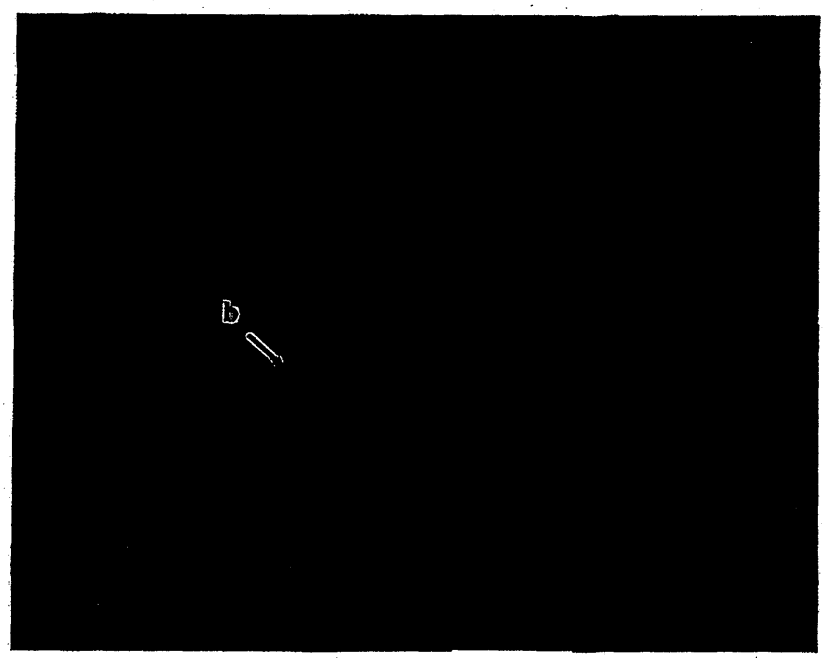


Photo 3 Structural aberration induced by
574 μg/mL for short-tem treatment without S9 mix in chromosomal aberration test
b: chromatid exchange (precipitation of the test substance was found on specimens)

APPENDIX 1

RESULTS OF OBSERVATION OF CHROMOSOMES
IN ACCORDANCE WITH "CONCERNING TESTING METHODS RELATING TO THE NEW CHEMICAL SUBSTANCES" ON JAPANESE TEST GUIDELINE

Table 1 Results of chromosomal aberration test (short-term treatments)

Name of test substance :

K06-1270

Treatment time (h)	S9 mix	Dose (μg/mL)	Number of cells with structural chromosomal aberrations (frequency%)							Number of gaps (frequency%)	Cell growth rate (%)	Number of cells with numerical chromosomal aberrations (frequency%)			
			Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others	Total number of cells with aberrations			Number of cells observed	Polyploids	Others	Total number of cells with aberrations
6 - 18	-	Negative control (D.W.)	100	2	1	0	0	0	3	1		100	0	0	0
			100	1	0	0	0	0	1	0	100	100	0	0	0
		0	200	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	1 (0.5)		200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	-	287 †	100	0	0	0	0	0	0	0	79.7	100	2	0	2
			100	2	1	0	0	0	2	1	73.7	100	1	0	1
			200	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.5)	(76.7)	200	3 (1.5)	0 (0.0)	3 (1.5)
6 - 18	-	574 †	100	1	3	0	0	0	4	0	55.7	100	0	0	0
			100	5	2	0	0	0	7	2	59.5	100	0	0	0
			200	6 (3.0)	5 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	11 (5.5)	2 (1.0)	(57.6)	200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	-	1150 †	100	0	0	0	0	0	0	0	55.1	100	4	0	4
			100	2	2	0	0	0	4	0	46.2	100	1	0	1
			200	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(50.7)	200	5 (2.5)	0 (0.0)	5 (2.5)
6 - 18	-	2300 †	100	3	1	0	0	0	4	0	37.3	100	0	0	0
			100	4	2	0	0	0	6	0	38.6	100	1	0	1
			200	7 (3.5)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	10 (5.0)	0 (0.0)	(38.0)	200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	-	Positive control (MMC)	100	41	54	0	0	0	68	2		100	0	0	0
			100	39	46	1	0	0	65	4		100	0	0	0
		0.1	200	80 (40.0)	100 (50.0)	1 (0.5)	0 (0.0)	0 (0.0)	133 (66.5)	6 (3.0)		200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	+	Negative control (D.W.)	100	0	0	0	0	0	0	0		100	1	0	1
			100	1	0	0	1	0	2	0	100	100	0	0	0
		0	200	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	2 (1.0)	0 (0.0)		200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	+	1150 †	100	1	1	0	0	0	1	0	80.3	100	2	0	2
			100	1	0	0	0	0	1	1	83.2	100	0	0	0
			200	2 (1.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (0.5)	(81.8)	200	2 (1.0)	0 (0.0)	2 (1.0)
6 - 18	+	2300 †	100	2	1	0	0	0	3	0	70.6	100	1	0	1
			100	0	1	0	0	0	1	0	65.9	100	0	0	0
			200	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(68.3)	200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	+	4590 †	100	2	1	0	0	0	3	0	62.4	100	0	0	0
			100	0	1	0	0	0	1	0	52.9	100	0	0	0
			200	2 (1.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(57.7)	200	0 (0.0)	0 (0.0)	0 (0.0)
6 - 18	+	Positive control (CPA)	100	12	26	0	0	0	34	0		100	0	0	0
			100	14	31	1	0	0	42	1		100	0	0	0
		6	200	26 (13.0)	57 (28.5)	1 (0.5)	0 (0.0)	0 (0.0)	76 (38.0)	1 (0.5)		200	0 (0.0)	0 (0.0)	0 (0.0)

Treatment time comprised treatment-time and recovery-time.
The number of aberrant cells at each dish was shown at the first and second lines. The total number of them was shown at the third line.
Cell growth rate at each dish was shown at the first and second lines. The average of them was shown at the third line.
D.W.: Distilled water
MMC: Mitomycin C
CPA: Cyclophosphamide monohydrate
†: Precipitation of the test substance was observed at the start and the end of the treatment and the end of the culture.

Table 2 Results of chromosomal aberration test (continuous treatment method)

Name of test substance : [redacted]

K06-1270

Treatment time (h)	Dose (μg/mL)	Number of cells with structural chromosomal aberrations (frequency%)							Number of gaps (frequency%)	Cell growth rate (%)	Number of cells with numerical chromosomal aberrations (frequency%)			
		Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others	Total number of cells with aberrations			Number of cells observed	Polyploids	Others	Total number of cells with aberrations
24 - 0	Negative control (D.W.)	100	0	0	0	0	0	0	0	100	100	1	0	1
		100	0	0	0	1	0	1	2		100	0	0	0
	0	200	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	2 (1.0)		200	1 (0.5)	0 (0.0)	1 (0.5)
24 - 0	143 †	100	3	0	0	0	0	3	0	77.2	100	1	0	1
		100	0	0	0	0	0	0	0	74.4	100	0	0	0
		200	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	(75.8)	200	1 (0.5)	0 (0.0)	1 (0.5)
24 - 0	287 †	100	2	0	0	0	0	2	0	59.0	100	1	0	1
		100	1	1	0	0	0	2	0	64.8	100	1	0	1
		200	3 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	(61.9)	200	2 (1.0)	0 (0.0)	2 (1.0)
24 - 0	574 †	100	2	2	0	0	0	3	0	37.7	100	0	0	0
		100	2	1	0	0	0	3	0	48.1	100	1	0	1
		200	4 (2.0)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.0)	0 (0.0)	(42.9)	200	1 (0.5)	0 (0.0)	1 (0.5)
24 - 0	1150 †	0								21.8	0			
		0								31.4	0			
		0								(26.6)	0			
24 - 0	Positive control (MMC)	100	36	61	0	1	0	72	2		100	1	0	1
		100	43	53	0	0	0	70	1		100	0	0	0
	0.05	200	79 (39.5)	114 (57.0)	0 (0.0)	1 (0.5)	0 (0.0)	142 (71.0)	3 (1.5)		200	1 (0.5)	0 (0.0)	1 (0.5)

Treatment time comprised treatment-time and recovery-time.

The number of aberrant cells at each dish was shown at the first and second lines. The total number of them was shown at the third line.

Cell growth rate at each dish was shown at the first and second lines. The average of them was shown at the third line.

D.W.: Distilled water

MMC: Mitomycin C

†: Precipitation of the test substance was observed at the start and the end of the treatment.

The specimens at 1150 μg/mL were not observed.

Name of test substance :

Table 3 Results of confirmation test (short-term treatment without S9 mix)

K06-1270

Treatment time (h)	S9 mix	Dose (μg/mL)	Number of cells with structural chromosomal aberrations (frequency%)							Number of gaps (frequency%)	Cell growth rate (%)	Number of cells with numerical chromosomal aberrations (frequency%)			
			Number of cells observed	Chromatid break	Chromatid exchange	Chromosome break	Chromosome exchange	Others	Total number of cells with aberrations			Number of cells observed	Polyploids	Others	Total number of cells with aberrations
6 - 18	-	Negative control (D.W.)	100	0	2	0	0	0	2	1	100	100	1	0	1
			100	3	0	0	0	0	3	0		100	3	0	3
		0	200	3 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (2.5)	1 (0.5)		200	4 (2.0)	0 (0.0)	4 (2.0)
6 - 18	-	143 †	100	0	2	0	0	0	2	0	91.4	100	3	0	3
			100	0	0	0	0	0	0	0	88.5	100	1	0	1
			200	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	(90.0)	200	4 (2.0)	0 (0.0)	4 (2.0)
6 - 18	-	287 †	100	4	1	0	0	0	5	0	70.3	100	4	0	4
			100	0	2	0	0	0	2	0	69.9	100	2	0	2
			200	4 (2.0)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	7 (3.5)	0 (0.0)	(70.1)	200	6 (3.0)	0 (0.0)	6 (3.0)
6 - 18	-	574 †	100	7	0	0	0	0	7	0	46.6	100	1	0	1
			100	5	1	0	0	0	6	0	50.5	100	0	0	0
			200	12 (6.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	13 (6.5)	0 (0.0)	(48.6)	200	1 (0.5)	0 (0.0)	1 (0.5)
6 - 18	-	1150 †	0								30.3	0			
			0								28.6	0			
			0								(29.5)	0			
6 - 18	-	2300 †	0								17.4	0			
			0								18.1	0			
			0								(17.8)	0			
6 - 18	-	Positive control (MMC)	100	35	53	0	0	0	66	2		100	0	0	0
			100	28	45	0	0	1	63	2		100	1	0	1
		0.1	200	63 (31.5)	98 (49.0)	0 (0.0)	0 (0.0)	1 (0.5)	129 (64.5)	4 (2.0)		200	1 (0.5)	0 (0.0)	1 (0.5)

Treatment time comprised treatment-time and recovery-time.

The number of aberrant cells at each dish was shown at the first and second lines. The total number of them was shown at the third line.

Cell growth rate at each dish was shown at the first and second lines. The average of them was shown at the third line.

Multiple that the number of aberration in the same aberration category appeared 10 or more was shown at others in structural chromosomal aberrations.

D.W.: Distilled water

MMC: Mitomycin C

†: Precipitation of the test substance was observed at the start and the end of the treatment and the end of the culture.

The specimens at 1150 and 2300 μg/mL were not observed.

APPENDIX 2

BACKGROUND DATA IN THE TESTING FACILITY

BACKGROUND DATA IN THE TESTING FACILITY

Negative control

Treatment method		Frequency of cells with chromosomal aberrations (%, mean±S.D.)	
		Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	1.9 ±1.13	0.5 ±0.63
	With S9 mix	0.9 ±0.63	0.7 ±0.51
24 hours continuous treatment		1.4 ±1.05	0.6 ±0.52

Treatment method		Range of frequency of cells with chromosomal aberrations (%, mean±3S.D.)	
		Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	0.0 ~ 5.3	0.0 ~ 2.4
	With S9 mix	0.0 ~ 2.8	0.0 ~ 2.2
24 hours continuous treatment		0.0 ~ 4.6	0.0 ~ 2.2

When the minimum range was below 0, it was shown "0.0".

Positive control

Treatment method		Substance	Dose (μg/mL)	Frequency of cells with chromosomal aberrations (%, mean±S.D.)	
				Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	MMC	0.1	58.7 ±7.55	0.4 ±0.52
	With S9 mix	CPA	6	33.9 ±6.93	0.5 ±0.48
24 hours continuous treatment		MMC	0.05	65.6 ±6.49	0.4 ±0.43

Treatment method		Range of frequency of cells with chromosomal aberrations (%, mean±2S.D.)	
		Structural aberration	Numerical aberration
Short-term treatment	Without S9 mix	43.6 ~ 73.8	0.0 ~ 1.4
	With S9 mix	20.0 ~ 47.8	0.0 ~ 1.5
24 hours continuous treatment		52.6 ~ 78.6	0.0 ~ 1.3

When the minimum range was below 0, it was shown "0.0".

The latest 20 test data completed by August 29, 2008 were used.

ATTACHMENT HEADER SHEET

Attachment Number 007

Attachment Name

Homogeneity, Stability And Concentration Analyses ...

Associated PMN Section Number

N/A

Does not contain CBI

Report Number

TSB2101224041049680

CERI

Receipt No. 827-08-D-3365

STUDY CODE: X18-0897

FINAL REPORT

HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF [redacted] FORMULATION

January 2009

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

X18-0897

STATEMENT

TITLE OF STADY

Homogeneity, Stability and Concentration Analyses of [redacted] Formulation (Study Code: X18-0897)

I, the undersigned, hereby declare that this report provides a correct English translation of the final report (Study Code: X18-0897, issued on January 8, 2009).

Yuji Kusune

Yuji Kusune, M.S.

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

July 2, 2009

Date

GLP STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Title: Homogeneity, Stability and Concentration Analyses of Formulation

Study Code: X18-0897

I, the undersigned, hereby declare that this study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)).

I also confirmed that this report accurately reflected the raw data and the test data were valid.

Study Director: Signed in original January 8, 2009

Yuji Kusune, M.S.

QUALITY ASSURANCE STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Title: Homogeneity, Stability and Concentration Analyses of Formulation

Study Code: X18-0897

This study was inspected by Quality Assurance Unit of Hita Laboratory, Chemicals Evaluation and Research Institute, Japan. The dates inspected and the dates reported these results to the study director and management are as follows

Phase	Date of Inspection	Date Reported to Study Director and Management
Protocol	August 21, 2008	August 21, 2008
Homogeneity and Stability Analyses of Test Substance Formulation	August 22, 2008	August 22, 2008
Confirmation of the Answer from Study Director (Protocol)	August 26, 2008	August 27, 2008
Amendment to Protocol	September 2, 2008	September 2, 2008
Concentration Analysis of Test Substance Formulation	September 5, 2008	September 5, 2008
Raw Data and Draft Final Report	January 6, 2009	January 6, 2009
Reinspection of Raw Data and Draft Final Report	January 7, 2009	January 7, 2009
Final Report	January 8, 2009	January 8, 2009

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study, and that the reported results accurately reflect obtained raw data.

Head, Quality Assurance Unit: Signed in original January 8, 2009

Ryuichiro Mizuguchi, B.S.

TABLE OF CONTENTS

Study Code: X18-0897
Test Substance Code: HR7578
Sponsor Code: I-0010

TITLE

Homogeneity, Stability and Concentration Analyses of Formulation

SPONSOR

TESTING FACILITY

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan
822, 3-chome, Ishii-machi, Hita, Oita 877-0061, Japan

PURPOSE OF STUDY

The purpose of this study is to determine homogeneity, stability and concentration of the test substance in formulation in "Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of LTO in Rats" (Study Code: B11-0897).

GLP COMPLIANCE

This study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)).

PERIOD OF STUDY

Commencement of Study:	August 19, 2008
Initiation of Examination (Initiation of Analysis):	August 22, 2008
Termination of Examination (Termination of Analysis):	September 8, 2008
Completion of Study:	January 8, 2009

STORAGE AND RETENTION PERIOD OF DATA

The raw data, protocol, amendment to protocol, study contract documents, test substance information, final report and other record documents will be retained in the archive of the Hita Laboratory of our organization for the same period of B11-0897 paper data. After termination of the retention period, any measures taken will be done so with the approval of the sponsor.

RETENTION OF ORIGINAL DOCUMENTS

An original protocol, an original amendment to protocol and an original final report will be retained at Hita Laboratory. The copies of their original that the study director will be recognized to be accurate copy will be sent to the sponsor.

STUDY DIRECTOR AND PERSONS CONCERNED WITH THE STUDY AND THE OPERATION

Study director:	Yuji Kusune, M.S.
Study staff:	Yuji Kusune, M.S. (Analysis of the test substance)
	Masaya Matsumoto, B.S. (Preparation of the test substance formulation)

APPROVAL BY AUTHOR

Study director: Signed in original — January 8, 2009

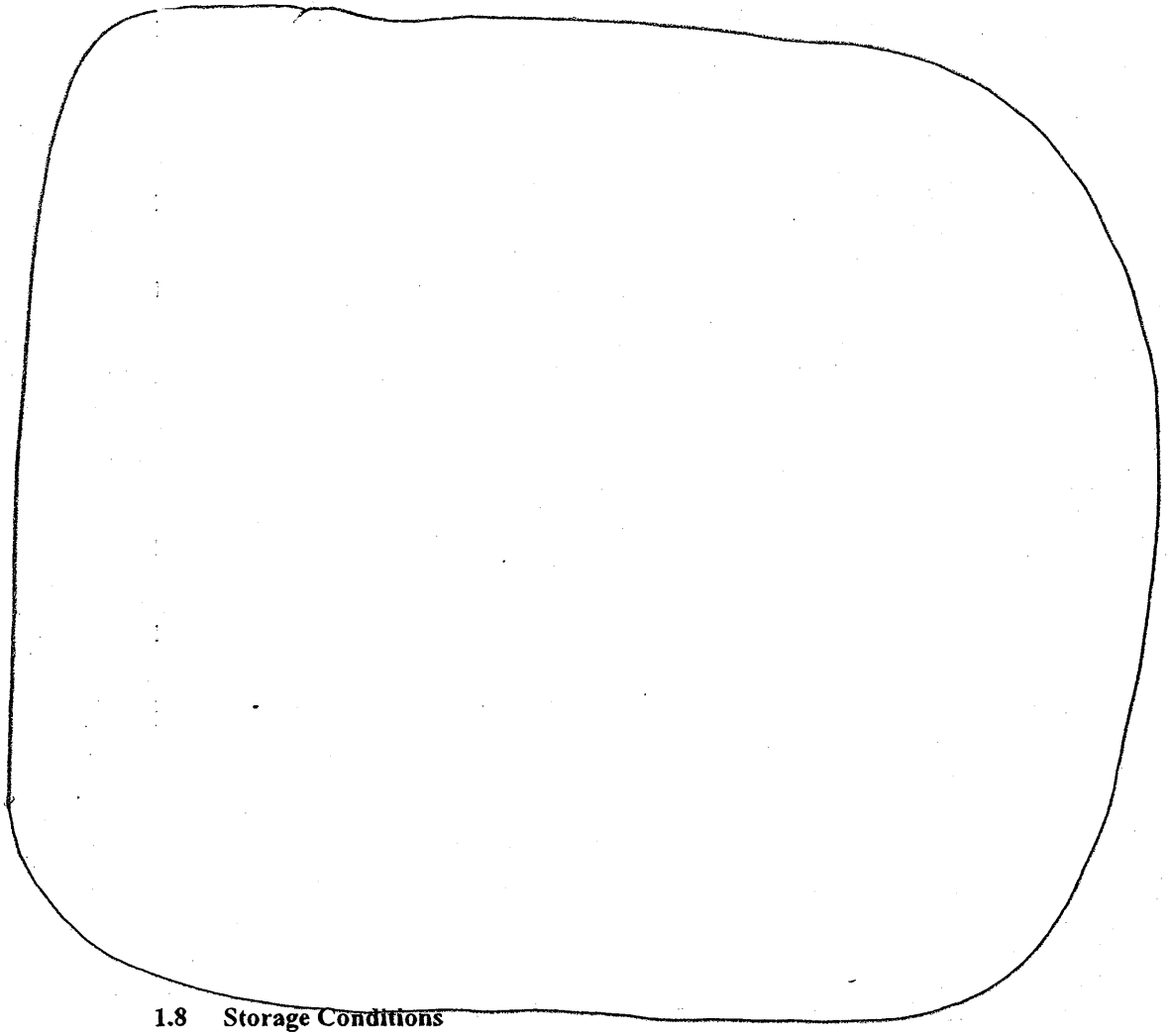
Yuji Kusune, M.S.
Analytical Chemistry Section
Hita Laboratory

SUMMARY

The test substance in 10.0 and 0.5 w/v% formulations was stable for 11 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 10.0, 2.5 and 0.5 w/v% dose formulations for subject study (Study Code: B11-0897) was acceptable level.

MATERIALS

1. TEST SUBSTANCE (INFORMATION PROVIDED BY THE SPONSOR)



1.8 Storage Conditions

Stored at room temperature (cabinet No. 7 in test substance storage room, tolerance temperature: 10-30°C). Actual temperature between received of test substance to termination of examination was 20.6-22.8°C. It satisfied tolerance.

1.9 Handling Precaution

Glove, mask, cap, protective glasses and lab coat were worn.

METHODS

1. SUBJECT STUDY

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of in Rats (Study Code:

B11-0897)

2. HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION

In the homogeneity analysis, the samples were taken (n=1) from the upper, middle and lower layers of formulations immediately after preparation, respectively. These samples were dried in weighing bottle, residues were weighed (n=1) (gravimetric analysis), and concentration of test substance was determined. In addition, because the results at first time preparation were not satisfied criteria for judgment (a rate to the nominal concentration for the actual concentration: 103-111% (10.0 w/v% formulation), 107-114% (0.5 w/v% formulation)), they were rejected. Formulations were prepared again, and the homogeneity analysis was carried out using formulations of second time preparation. At sampling from formulation, Multipette plus 4981 was used at first time preparation, and measuring pipette was used at second time preparation.

In the stability analysis, the formulations were stored at cold and dark place for 11 days, and the sample was taken (n=1) from the middle layer of the formulations at point of measurement (after 7 days and 12 days after preparation). These samples were dried in weighing bottle, residues were weighed (n=1), and concentration of test substance was determined.

In the concentration analysis, the samples were taken (n=1) from the middle layer of dose formulations immediately after preparation for subject study. These samples were dried in weighing bottle, residues were weighed (n=1), and concentration of test substance was determined.

2.1 The Test Substance Formulation

1) Homogeneity and Stability Analyses

(1) Concentration

10.0 and 0.5 w/v%

(2) Preparation Method

The test substance was accurately weighed and mixed with purified water to prepare 10.0 w/v% formulation. 0.5 w/v% formulation was diluted from 10.0 w/v% formulation with purified water.

Preparation	Test substance sampling weight (g)	10.0 w/v% formulation final volume (mL)	10.0 w/v% formulation sampling volume (mL)	0.5 w/v% formulation final volume (mL)
First time (reject)	5.00	50	10	200
Second time	10.00	100	15	300

Vehicle: purified water (Lot No. 080613A, Takasugi Pharmaceutical Co., Ltd.)

2) Concentration Analysis

The 10.0, 2.5 and 0.5 w/v% dose formulations at first preparation for subject study were used.

2.2 Outline of Analytical Method

The analytical method was decided, according to results of validation of the analytical method on non-GLP at the test facility. In addition, theoretical value of sampling weight from formulations was 0.1 g (10.0 w/v% formulation: 1 mL, 2.5 w/v% formulation: 4 mL, 0.5 w/v% formulation: 20 mL).

1) Validation of the Analytical Method

(1) Specificity

The weighing bottle was dried for 31 minutes under reduced pressure in desiccator (desiccant: silica gel) and weighed (weight before adding of blank). After adding of 20 mL of purified water (solvent and vehicle blank) to weighing bottle (n=3), there were evaporated for 60 minutes by hot plate (NA-1, AS ONE corporation, set temperature 200°C). There were dried for 78 minutes under reduced pressure in desiccator and weighed (weight after adding of blank).

The weights of residue in solvent and vehicle blank were 0.0000, 0.0000 and 0.0002 g. Because these results were less than 0.2% of theoretical value, it was confirmed that there were no effect to result.

(2) Accuracy (Recovery Rate) and Repeatability

The weighing bottle was dried for 31 minutes under reduced pressure in desiccator and weighed (weight before adding of test substance). Approximately 0.1 g of the test substance and 20 mL of purified water was added to weighing bottle (n=6), there were evaporated for 60 minutes by hot plate. There were dried for 78 minutes under reduced pressure in desiccator and weighed (weight after adding of test substance).

Accuracy (recovery rate) was 101,100,101,101,101 and 101% and repeatability was 0.4%. It was confirmed that the result of accuracy and repeatability satisfied criteria for judgment (accuracy: within 100±10%, repeatability: less than 5%).

2) Pre-Treatment

Formulations were mixed well using a magnetic stirrer. In addition, the weighing bottle was used that dried for 30 minutes or more under reduced pressure in desiccator and weighed (weight before adding of formulation).

(1) 10.0 w/v% Formulation (Homogeneity, Stability and Concentration Analyses)

Accurate 1 mL of formulation was sampling to weighing bottle. After adding 19 mL of purified water, it was evaporated for 60 minutes by hot plate. It was dried for 80 minutes or more under reduced pressure in desiccator and weighed (weight after adding of formulation).

(2) 2.5 w/v% Formulation (Concentration Analysis)

Accurate 4 mL of formulation was sampling to weighing bottle. After adding 16 mL of purified water, it was evaporated for 60 minutes by hot plate. It was dried for 80 minutes or more under reduced pressure in desiccator and weighed (weight after adding of formulation).

(3) 0.5 w/v% Formulation (Homogeneity, Stability and Concentration Analyses)

Accurate 20 mL of formulation was sampling to weighing bottle. It was evaporated for 60 minutes by hot plate. It was dried for 80 minutes or more under reduced pressure in desiccator and weighed (weight after adding of formulation).

3) Instrument for Weighing

Electron analysis balance: LA230S (Sartorius K.K.)

2.3 Data Processing

1) Detection Value

The weight (g) measured with electron analysis balance was used the detection value.

2) Calculation of the Test Substance Concentration in Formulation

Concentration of test substance in each sample (C: w/v%) was calculated with the equation shown below and rounded off to three significant figures.

$$W_2 = W_1 - W_0$$

$$C = \frac{W_2}{V_0} \times 100$$

W_0: weight before adding of formulation (g)

W_1: weight after adding of formulation (g)

W_2: weight of residue (g)

V_0: volume of formulation (mL)

2.4 Criteria for Judgment

1) Homogeneity Analysis

The test substance was judged as homogeneous dispersion in vehicle if a coefficient of variation (CV) was within 5%. The CV was calculated using the following equation:

$$CV(\%) = \frac{\text{Standard deviation for concentration of test substance in each layer}}{\text{Mean concentration of test substance in each layer}} \times 100$$

2) Stability Analysis

The test substance was judged as stable state in vehicle if a rate to the nominal concentration for the actual concentration (R.N.) and a rate to the mean concentration immediately after preparation for the actual concentration (R.P.) were within the range of 100±10%. The R.N. and R.P. were calculated using the following equation:

$$\text{R.N.}(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

$$\text{R.P.}(\%) = \frac{\text{Actual concentration}}{\text{Mean concentration immediately after preparation}} \times 100$$

3) Concentration Analysis

It was confirmed that R.N. was within the range of 100±10%. The R.N. was calculated using the following equation:

$$\text{R.N.}(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED RELIABILITY OF STUDY RESULTS

There were no factors that might have affected the reliability of the study data.

RESULTS AND DISCUSSION

1. RESULTS

1.1 Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

1) Homogeneity and Stability Analyses

The results of homogeneity and stability analyses of the test substance formulation are shown in Table 1.

(1) Homogeneity Analysis

CV of 10.0 and 0.5 w/v% formulations were 1.0 and 0.3%, respectively. The results satisfied criteria for judgment.

(2) Stability Analysis

a) 10.0 w/v% Formulation

At immediately after preparation, R.N. were 101 to 103%.

At 7 days after preparation, R.N. was 100%, and R.P. was 98.0%.

At 12 days after preparation, R.N. was 101%, and R.P. was 99.0%.

All the results of R.N. and R.P. satisfied criteria for judgment.

b) 0.5 w/v% Formulation

At immediately after preparation, R.N. were 92.6 to 93.2%.

At 7 days after preparation, R.N. was 910%, and R.P. was 98.1%.

At 12 days after preparation, R.N. was 92.0%, and R.P. was 99.1%.

All the results of R.N. and R.P. satisfied criteria for judgment.

2) Concentration Analysis

The results of concentration analysis of the test substance formulation are shown in Table 2.

R.N. of 10.0, 2.5 and 0.5 w/v% dose formulations were 96.0 to 97.9%. All the results satisfied criteria for judgment.

2. DISCUSSION

The test substance in 10.0 and 0.5 w/v% formulations was stable for 11 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 10.0, 2.5 and 0.5 w/v% dose formulations for subject study was acceptable level.

Table 1 Homogeneity and stability analyses of the test substance formulation

Nominal conc. (w/v%)	Time point of measurement	Layer of measurement	Actual conc. (w/v%)	R.N. (%)	Mean conc. (w/v%)	R.P. (%)	CV (%)
10.0	Immediately after preparation	Upper	10.3	103	10.2	-	1.0
		Middle	10.1	101			
		Lower	10.2	102			
	7 days after preparation	Middle	10.0	100	-	98.0	-
	12 days after preparation	Middle	10.1	101	-	99.0	-
0.5	Immediately after preparation	Upper	0.464	92.8	0.464	-	0.3
		Middle	0.466	93.2			
		Lower	0.463	92.6			
	7 days after preparation	Middle	0.455	91.0	-	98.1	-
	12 days after preparation	Middle	0.460	92.0	-	99.1	-

R.N.: Rate to the nominal concentration

R.P.: Rate to the concentration measured immediately after preparation

CV: Coefficient of variation

Table 2 Concentration analysis of the dose formulation

Date of analysis	Nominal conc. (w/v%)	Actual conc. (w/v%)	R.N. (%)
September 5, 2008	10.0	9.79	97.9
	2.5	2.40	96.0
	0.5	0.481	96.2

R.N.: Rate to the nominal concentration

ATTACHMENT HEADER SHEET

Attachment Number 008

Attachment Name

Mutagenicity Test ...

Associated PMN Section Number

N/A

Does not contain CBI

Report Number

TSB2101224041049680

CERI

STUDY CODE: K01-4186

Receipt No. 836-08-T-5900

FINAL REPORT

MUTAGENICITY TEST OF [redacted]
USING MICROORGANISMS

September 2008

CERI Hita
Chemicals Evaluation and Research Institute, Japan

STATEMENT

TITLE OF STUDY

Mutagenicity Test of [redacted] Using Microorganisms (Study Code: K01-4186)

I, the undersigned, hereby declare that this report provides a correct English translation of the final report (Study Code: K01-4186, issued on September 30, 2008) audited by Quality Assurance Unit of CERI Hita, Chemicals Evaluation and Research Institute, Japan.

Shinya Wakamatsu — October 16, 2009

Shinya Wakamatsu
CERI Hita
Chemicals Evaluation and Research Institute, Japan

Date

ALL CIRCLED INFORMATION
IS CONFIDENTIAL

GLP STATEMENT

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

Title: Mutagenicity Test of Using Microorganisms
Study Code: K01-4186

I, the undersigned, hereby declare that this study was conducted in compliance with "Standards to be observed by Testing Institutions for Toxicity Investigations" (Ministry of Labor, Notification No.76, September 1, 1988; partially revised on March 29, 2000) and "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (2003.11.17) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Principles of Good Laboratory Practice" (November 26, 1997).

Management: Signed in original September 30, 2008
Takaharu Hara

GLP STATEMENT

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

Title: Mutagenicity Test of [redacted] Using Microorganisms
Study Code: K01-4186

I, the undersigned, hereby declare that this study was conducted in compliance with "Standards to be observed by Testing Institutions for Toxicity Investigations" (Ministry of Labor, Notification No.76, September 1, 1988; partially revised on March 29, 2000) and "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (2003.11.17) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Principles of Good Laboratory Practice" (November 26, 1997).

I also confirmed that this report accurately reflected the raw data and the test data were valid.

Study Director: Signed in original September 30, 2008
Wakamatsu Shinya

ALL CIRCLED INFORMATION
IS CONFIDENTIAL

K01-4186
1/2

QUALITY ASSURANCE STATEMENT

CERI Hita
Chemicals Evaluation and Research Institute, Japan

Title: Mutagenicity Test of Using Microorganisms
Study Code: K01-4186

This study was inspected by Quality Assurance Unit of CERI Hita, Chemicals Evaluation and Research Institute, Japan. The dates inspected and the dates reported these results to the study director and management are as follows.

Phase	Date of Inspection	Date Reported to Study Director and Management
Protocol	September 2, 2008	September 2, 2008
Approval of Protocol	September 4, 2008	September 4, 2008
Preparation of Test Substance	September 5, 2008	September 5, 2008
Treatment of Test Strains	September 5, 2008	September 5, 2008
Culture Condition and Observation and Colony Count	September 8, 2008	September 8, 2008
Test Strains Pre-culture	September 8 and 9, 2008	September 9, 2008
Confirmation of the Answer from Study Director (Protocol)	September 10, 2008	September 10, 2008
Raw Data and Draft Final Report	September 29, 2008	September 29, 2008
Reinspection of Raw Data and Draft Final Report	September 29, 2008	September 29, 2008
Final Report	September 30, 2008	September 30, 2008

The inspection result of following phase was reported to the study director and management based on the report of process-based inspection relevant to this study type and timeframe.

Phase	Date of Inspection	Date Reported to Study Director and Management
Examination of Solubility of the Test Substance	October 2, 2007	September 30, 2008
Preparation and Management of Positive Control Substance	May 22, 2008	September 30, 2008

Preparation of Medium and Reagent	December 10 and 11, 2007 and January 15, 2008	September 30, 2008
Management of Test Strains	April 21, 22, 29 and 30 and May 1, 2008	September 30, 2008

I, the undersigned, hereby declare that this study was conducted in compliance with "Standards to be observed by Testing Institutions for Toxicity Investigations" (Ministry of Labor, Notification No.76, September 1, 1988; partially revised on March 29, 2000), "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (2003.11.17) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Principles of Good Laboratory Practice" (November 26, 1997).
This study was also conducted in compliance with "Standards for Toxicity Investigations" (Ministry of Labor, Notification No.77, September 1, 1988 and Notification No.67, June 2, 1997) and "Procedures of Mutagenicity Test Using Microorganisms and Evaluation of Test Results" (Ministry of Labor, Official Notification, February 8, 1999) and "III Mutagenicity test" of "Reverse-Mutation Assay in Bacteria" prescribed in "Testing Methods Relating to the New Chemical Substances" (Notification No. 1121002 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 2 (2003.11.13) of the Manufacturing Industries Bureau, METI & No.031121002 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Guidelines for Testing of Chemicals, 471, Bacterial Reverse Mutation Test"(July 21, 1997).

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study and that the reported results accurately reflect the raw data obtained.

Head, Quality Assurance Unit: Signed in original September 30, 2008
Ryuichiro Mizuguchi

TABLE OF CONTENTS

Study Code: K01-4186
Test Substance Code: HR7578
Sponsor Code: I-0010

TITLE

Mutagenicity Test of Using Microorganisms

SPONSOR

TESTING FACILITY

CERI Hita
Chemicals Evaluation and Research Institute, Japan
822, 3-chome, Ishii-machi, Hita, Oita 877-0061, Japan

PURPOSE OF STUDY

The ability of the test substance to induce mutations was investigated by using *Salmonella typhimurium* and *Escherichia coli*.

TESTING METHOD

This study was conducted in compliance with "Standards for Toxicity Investigations" (Ministry of Labor, Notification No.77, September 1, 1988 and Notification No.67, June 2, 1997) and "Procedures of Mutagenicity Test Using Microorganisms and Evaluation of Test Results" (Ministry of Labor, Official Notification, February 8, 1999) and "III Mutagenicity test" of "Reverse-Mutation Assay in Bacteria" prescribed in "Testing Methods Relating to the New Chemical Substances" (Notification No. 1121002 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 2 (2003.11.13) of the Manufacturing Industries Bureau, METI & No.031121002 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Guidelines for Testing of Chemicals, 471, Bacterial Reverse Mutation Test"(July 21, 1997).

GLP COMPLIANCE

I, the undersigned, hereby declare that this study was conducted in compliance with "Standards to be observed by Testing Institutions for Toxicity Investigations" (Ministry of Labor, Notification No.76, September 1, 1988; partially revised on March 29, 2000), "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" (Notification No. 1121003 of the Pharmaceutical and Food Safety

Bureau, MHLW, No. 3 (2003.11.17) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)) and "OECD Principles of Good Laboratory Practice" (November 26, 1997).

PERIOD OF STUDY

Commencement of Study:	August 29, 2008
Initiation of Experiment (Initiation of Treatment of Dose Finding Test):	September 5, 2008
Completion of Experiment (Completion of Colony Count):	September 16, 2008
Completion of Study:	September 30, 2008

STORAGE AND RETENTION PERIOD OF DATA

Raw data, protocol, letter of test request, questionnaire, final report and other documentation records will be retained in the archives and the test substance will be retained at the test substance storage room of the testing facility for 10 years after the date of the notification specified under Item 1 of Article 57-3 of Industrial Safety & Health Law. Date of the notification will be communicated from the sponsor to the testing facility. They also will be retained for 10 years after the date of the notification specified under Article 4, Paragraph 1 or Paragraph 2, Article 4-2, Paragraph 2, Paragraph 3 or Paragraph 8, Article 5-4, Paragraph 2, Article 24, Paragraph 2 or Article 25-3, Paragraph 2 of Notification on Testing Methods Relating to the New Chemical Substances. The sponsor will communicate the date of the notification to the testing facility. Treatment of data after termination of the retention period will be carried out with the approval of the sponsor.

RETENTION OF ORIGINAL DOCUMENTS

An original and a duplicate of protocol were drawn up. The former will be retained at the testing facility. The latter was sent to the sponsor.

An original final report is drawn up and will be retained at the testing facility. A copy of the original final report that was recognized to be an accurate copy by the study director will be sent to the sponsor.

STUDY DIRECTOR AND PERSONS CONCERNED WITH THE STUDY AND THE OPERATION

Study Director:	Shinya Wakamatsu Section 3, Hita Laboratory
Study Staff:	Shozo Ogura, Shinya Wakamatsu, and Erika Mizuguchi Section 3, Hita Laboratory (Preparation of the test substance, count of revertant colonies)
Management:	Takaharu Hara Hita Laboratory
Person in Charge of Storage of Archives:	Shizuka Kouda General Affairs Section, Hita Laboratory
Person in Charge of Test Substance Management:	Haruhiko Tajima Section 1, Hita Laboratory

AUTHOR OF FINAL REPORT

Study Director: Signed in original September 30, 2008

Wakamatsu Shinya

SUMMARY

The ability of to induce mutations was investigated using *Salmonella typhimurium* strains TA100, TA1535, TA98 and TA1537 and *Escherichia coli* strain WP2*uvrA* with a pre-incubation method in the presence and absence of a metabolic activation system (S9 mix).

As a result, the mutagenicity of the test substance was judged to be negative because the numbers of revertant colonies in the test substance treatment groups were less than two times that in each negative control in all test strains with and without S9 mix.

Therefore, it is concluded that has no ability to induce mutations under the present test conditions.

MATERIALS AND METHODS

1. TEST SUBSTANCE AND POSITIVE CONTROL SUBSTANCES

8) Storage conditions

Tightly sealed and stored at room temperature (cabinet No. 1 in the test substance storage room, permissible range: 10-30°C).

9) Precautions

Gloves, a mask, a head cap, safety glasses and a lab coat were worn.

1.2 Positive Controls

Name	Manufacturer	Lot No.	Appearance	Purity	Grade
AF-2*1	Wako Pure Chemical Industries, Ltd.	WAP0369	Red-yellow crystalline powder	100.2%	Special grade
NaN_3*2	Wako Pure Chemical Industries, Ltd.	KLN3948	White crystalline powder	99.8%	Special grade
ICR-191*3	Polysciences, Inc.	534652	Yellow crystalline powder	—	—
2AA*4	Wako Pure Chemical Industries, Ltd.	ASM1101	Yellow-green-brown powder	97.4%	—

*1: 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide

*2: Sodium azide

*3: 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine·2HCl

*4: 2-Aminoanthracene

1) Storage conditions

Stored in a cool and dark place (refrigerator No. 005 in test substance storage room of the main building, permissible range: 1-10°C).

2) Precautions

Gloves, a mask, a head cap, safety glasses and a lab coat were worn.

2. BACTERIAL STRAINS

2.1 Strains and Reason for Selection

Salmonella typhimurium strains TA100, TA1535, TA98 and TA1537 and *Escherichia coli* strain WP2*uvrA* were used. *Salmonella typhimurium* strains and *Escherichia coli* strain were supplied from Dr. Taijiro Matsushima, Japan Bioassay Research Center, on March 13, 2003 and on September 20, 2003, respectively. These test strains have been recommended to use for the mutagenicity test using microorganisms in "Standards for Toxicity Investigations", "Testing Methods Relating to the New Chemical Substances" and "OECD Guidelines for Testing of Chemicals, 471, Bacterial Reverse Mutation Test".

2.2 Storage

Amino acid requirement, sensitivity to ultraviolet-rays, rfa membrane mutation, presence or absence of plasmid pKM101 and negative and positive control values of test strains were examined in the testing facility. Dimethyl sulfoxide (DMSO, Lot No. VV035, 100.0% in purity, spectrophotometric grade, DOJINDO Laboratories) was added to fresh overnight cultures of the test strains which had been confirmed to have these properties at a volume ratio of 0.9:10. The mixture was frozen as a stock culture in an ultra-deep freezer (MDF-293AT in the Ames test room No. 1 of the main building, SANYO Electric Biomedical Co., Ltd.) below -80°C. The mixture was thawed just before use.

3. MEDIUM AND S9 MIX

3.1 Medium

1) Minimal glucose agar plate

Tesmedia AN (Oriental Yeast Co., Ltd.) was used.

Lot No.: ANI410GX (manufactured on July 8, 2008)

2) Soft agar

A solution containing 0.5 mM histidine and 0.5 mM biotin for *S. typhimurium* strains or 0.5 mM tryptophan for *E. coli* strain was added to a soft agar solution containing 0.6 w/v% agar (Bacto Agar, Lot No. 6080253, Difco Laboratories) and 0.5 w/v% NaCl at a volume ratio of 1 to 10.

3.2 S9 Mix

1) Rat liver S9

S9 (Lot No. 08071104, manufactured on July 11, 2008, Oriental Yeast Co., Ltd.) prepared from the liver of 7 week-old male SD rats (body weight: 208.3±7.9 g) treated with a combination of phenobarbital and 5, 6-benzoflavone was used. The S9 was cryopreserved in an ultra-deep freezer (MDF-293AT in the Ames test room No. 1 of the main building, SANYO Electric Biomedical Co., Ltd.) below -80°C

until use. S9 was thawed just before use.

2) Composition of S9 mix

S9 mix was prepared using Cofactor I® (Lot No. 999801, Oriental Yeast Co., Ltd.) for S9 mix immediately before use.

One milliliter of S9 mix consisted of 8 μmol $MgCl_2$, 33 μmol KCl, 5 μmol Glucose-6-phosphate, 4 μmol NADPH, 4 μmol NADH, 100 μmol sodium-phosphate buffer (pH 7.4) and 0.1 mL of S9.

4. PRE-CULTURES OF THE TEST STRAINS

Thirty microliters (for TA100), 5-μL (for WP2*uvrA*), and 20-μL (for TA98, TA1535 and TA1537) aliquots of frozen stock culture of bacterial strains were respectively inoculated to 11 mL of Nutrient broth No. 2 (Lot No. 464616, OXOID Ltd.) in each L tube (volume: 27 mL). The culture was incubated at 37±0.5°C for 9 hours by shaking at about 50 times/minute in a seesaw type of shaker (MONOSIN-IIA, Taitec Corporation). The number of viable cells was calculated from O.D. value at 660 nm measured by a photo meter (miniphoto 518R, Taitec Corporation) at the end of incubation to calculate the number of viable cells. It was confirmed that the numbers of viable cells were more than 2.3×10^9 cells/mL in *Salmonella typhimurium* and more than 3.8×10^9 cells/mL in *Escherichia coli* strain. When the numbers of viable cells were more than 2.7×10^9 cells/mL in *Salmonella typhimurium* and more than 4.2×10^9 cells/mL in *Escherichia coli* strain, the O.D. value was measured at 660 nm by a photo meter (the same above) and were adjusted with Nutrient broth No. 2 at 2.3-2.7×10^9 cells/mL and at 3.8-4.2×10^9 cells/mL, respectively. The culture was used without adjusting when the *Salmonella typhimurium* strains were in the range of 2.3-2.7×10^9 cells/mL. The final numbers of prepared viable cells is shown below:

Test	TA100	TA1535	WP2*uvrA*	TA98	TA1537
Dose finding test	2.6	2.5	4.0	2.6	2.3
Main test-1	2.6	2.5	4.0	2.6	2.6
Main test-2	2.7	2.6	4.0	2.6	2.4

($\times10^9$cells/mL)

5. PREPARATION OF TEST SUBSTANCE AND POSITIVE CONTROL SUBSTANCES

5.1 Preparation of Test Substance

1) Solvent

Distilled water (for injection, Lot No. K7D79 (dose finding test) and K8B81 (main test-1 and main test-2, Otsuka Pharmaceutical Factory Inc.).

2) Reason for selection of solvent

The test substance was uniform suspended in distilled water (50.0 mg/mL) and in DMSO (50.0 mg/mL). The test substance suspension of 50.0 mg/mL prepared with distilled water and DMSO was considered to be stable from the facts that there was no change in color nor heat generation at room temperature within 2 hours after preparation. Therefore, distilled water was preferably selected as a solvent because distilled water had less effect on test strains than DMSO.

3) Preparation method

Distilled water was added to the test substance and mixed by a tube mixer to make a 50.0 mg/mL suspension. The test substance suspension was diluted with the same solvent to give each required concentration.

4) Preparation time

The test substance suspension was prepared immediately before use, kept under yellow lamps at room temperature and used within 2 hours.

5.2 Preparation of Positive Controls

1) Preparation method

NaN_3 was dissolved in distilled water (distilled water for injection, Lot No. K7D79, Otsuka Pharmaceutical Factory Inc.). AF-2, ICR-191 and 2AA were dissolved in DMSO (Lot No. VV035, 100.0% in purity, spectrophotometric grade, DOJINDO Laboratories).

2) Storage conditions

Positive control solutions were stored in an ultra-deep freezer (MDF-293AT in the Ames test room No. 1 of the main building, SANYO Electric Biomedical Co., Ltd.) below -80°C. The solutions were thawed before use.

6. METHODS

A dose finding test and two main tests were performed by the pre-incubation method with and without S9 mix. Triplicate plates were used for the negative control group, and duplicate plates for the test substance treatment group at each dose and the positive control group in the dose finding test. Triplicate plates were used for the negative and positive control groups and the test substance treatment group at each dose in the main tests. The test code number, name of test strain, presence or absence of S9 mix and dose level were noted on each plate.

6.1 Procedures

After 0.1 mL of the test substance solution, solvent or the positive control solution, 0.5 mL of 0.1 M sodium phosphate buffer (pH 7.4) or S9 mix and 0.1 mL of the bacterial culture were added to a test tube, the mixture was shaken at 37±0.5°C for 20 minutes. Two milliliters of the soft agar were then added to each tube and the

mixture was poured onto a minimal glucose agar plate. The number of revertant colonies was counted after incubation at 37±0.5°C for 48 hours.

6.2 Sterility

The highest concentration of the test substance solution (0.1 mL) and S9 mix (0.5 mL) were respectively mixed with 2 mL of the soft agar and were poured onto each minimal glucose agar plate in order to examine bacterial contamination. Bacterial contamination was judged with that plate after 48 hours incubation of 37±0.5°C.

6.3 Negative Control and Positive Controls

The solvent used in the tests was employed as a negative control and the following positive controls were used for each bacterial strain.

	TA100	TA1535	WP2*uvrA*	TA98	TA1537
–S9 mix	AF-2	NaN_3	AF-2	AF-2	ICR-191
	0.01	0.5	0.01	0.1	0.5
+S9 mix	2AA	2AA	2AA	2AA	2AA
	1	2	10	0.5	2

(Unit: μg/plate)

6.4 Dose Selection

1) Dose finding test

A total of 6 doses consisting of 5000 μg/plate as the highest dose and 5 lower doses diluted with a geometric progression of 4 were employed.

2) Main test-1 and main test-2

The results of the dose finding test showed that the number of revertant colonies in the test substance treatment groups in all test strains with and without S9 mix was less than twice that in the solvent control. The bacterial growth inhibition was not observed in any test strain. The precipitation of the test substance was not observed at any doses in the groups of treatment with and without S9 mix.

Therefore, a total of 5 doses, the highest dose was selected at 5000 μg/plate and lower 4 doses of 2500, 1250, 625 and 313 μg/plate diluted with a geometric progression of 2, were employed in all test strains with and without S9 mix in the main test-1. Main test-2 was carried out to same dose for the main test-1 in order to the reproducibility as a result of the main test-1.

7. OBSERVATION AND COLONY COUNTING

7.1 Observation

The precipitation of the test substance was observed by macroscopically and the bacterial growth inhibition was observed by using a stereomicroscope at the end of the incubation period.

7.2 Colony Counting

The number of colonies was counted by using a colony analyzer (CA-11D, System Science Ltd.) for all plates. Square correction and miss counting correction were performed in colony analyzer.

8. JUDGEMENT CRITERIA OF TEST RESULTS

The test substance was judged positive when the number of revertant colonies increased to twice or more that in the negative control in a concentration-dependent manner and also the reproducibility of the test results was obtained. In all other cases, it was judged negative. Any statistical methods were not used.

FACTORS AFFECTED RELIABILITY OF TEST

Lot No. of distilled water for solvent was K7D79 in the protocol, however, lot No. K8B81 of distilled water was used in the main test-1 and the main test-2 because lot No. K7D79 of distilled water was spent. It was judged that this was not affected the reliability of the test. Others, there were no factors that might have affected the reliability of the test.

TEST RESULTS

1. DOSE FINDING TEST

The test result and the dose-response curves are shown in Table 1, Fig. 1 and Fig. 2.
The number of revertant colonies in the test substance treatment groups in all test strains with and without S9 mix was less than twice that in the solvent control. The bacterial growth inhibition was not observed in any test strain. The precipitation of the test substance was not observed at any doses in the groups of treatment with and without S9 mix.

2. MAIN TEST-1

The test result and the dose-response curves are shown in Table 2, Fig. 3 and Fig. 4.
The number of revertant colonies in the test substance treatment groups in all test strains with and without S9 mix was less than twice that in the solvent control. The bacterial growth inhibition was not observed in any test strain. The precipitation of the test substance was not observed at any doses in the groups of treatment with and without S9 mix.

3. MAIN TEST-2

The test result and the dose-response curves are shown in Table 3, Fig. 5 and Fig. 6.
The number of revertant colonies in the test substance treatment groups in all test strains with and without S9 mix was less than twice that in the solvent control. The bacterial growth inhibition was not observed in any test strain. The precipitation of the test substance was not observed at any doses in the groups of treatment with and without S9 mix.

DISCUSSION AND CONCLUSION

The mutagenicity of the test substance was judged to be negative because the number of the revertant colonies in the test substance treatment groups in all test strains was less than two times that in the negative control regardless of the presence or absence of S9 mix.
The number of the revertant colonies in the positive controls was two times or more than that in the negative control. The test results showed that the numbers of revertant colonies in the negative control and the positive control groups were within the range of the historical data in the testing facility. It was also confirmed that the test system was free from bacterial contamination, which indicates the test results to be valid.
From the above results, it was concluded that had no ability to induce mutations under the present test conditions.

Table 1 Results of the dose finding test

Test substance: [redacted]

Test Period		From September 5, 2008 to September 8, 2008				
With(+)or without(-) S9 mix	Test substance dose (μg/plate)	Number of revertant colonies per plate				
		Base-pair substitution type			Frameshift type	
		TA100	TA1535	WP2*uvrA*	TA98	TA1537
-S9 mix	Negative control	99 118 (107) 105	13 11 (10) 7	30 22 (27) 28	15 22 (17) 13	6 15 (11) 11
	4.88	104 101 (103)	8 16 (12)	25 27 (26)	22 21 (22)	7 5 (6)
	19.5	110 94 (102)	14 7 (11)	31 19 (25)	26 19 (23)	10 10 (10)
	78.1	95 103 (99)	11 10 (11)	15 29 (22)	30 22 (26)	15 11 (13)
	313	108 115 (112)	8 12 (10)	23 28 (26)	15 21 (18)	12 12 (12)
	1250	101 101 (101)	15 15 (15)	29 25 (27)	18 23 (21)	8 13 (11)
	5000	105 90 (98)	13 11 (12)	27 21 (24)	22 28 (25)	10 10 (10)
+S9 mix	Negative control	141 108 (116) 99	16 8 (11) 8	29 31 (34) 42	34 43 (38) 37	25 25 (24) 21
	4.88	107 115 (111)	14 14 (14)	16 19 (18)	31 33 (32)	19 19 (19)
	19.5	99 124 (112)	10 15 (13)	34 34 (34)	38 31 (35)	21 19 (20)
	78.1	115 105 (110)	6 14 (10)	30 34 (32)	25 28 (27)	25 15 (20)
	313	96 102 (99)	7 8 (8)	29 31 (30)	27 38 (33)	23 30 (27)
	1250	115 124 (120)	12 12 (12)	27 36 (32)	27 27 (27)	29 23 (26)
	5000	98 104 (101)	13 11 (12)	18 31 (25)	30 23 (27)	18 14 (16)
Positive control -S9 mix	Chemical	AF-2	NaN_3	AF-2	AF-2	ICR-191
	Dose(μg/plate)	0.01	0.5	0.01	0.1	0.5
	Number of revertant colonies/plate	649 637 (643)	363 372 (368)	269 288 (279)	567 594 (581)	1529 1571 (1550)
Positive control +S9 mix	Chemical	2AA	2AA	2AA	2AA	2AA
	Dose(μg/plate)	1	2	10	0.5	2
	Number of revertant colonies/plate	867 906 (887)	230 181 (206)	530 526 (528)	291 269 (280)	234 234 (234)

[Notes]
- ( ): The mean number of colonies per plate.
- AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
- NaN_3: Sodium azide
- ICR-191: 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)aminopropylamino]acridine·2HCl
- 2AA: 2-Aminoanthracene

Table 2 Results of the main test-1

Test substance: [redacted]

Test Period		From September 9, 2008 to September 11, 2008				
With(+)or without(-) S9 mix	Test substance dose (μg/plate)	Number of revertant colonies per plate				
		Base-pair substitution type			Frameshift type	
		TA100	TA1535	*WP2uvrA*	TA98	TA1537
−S9 mix	Negative control	97 98 (104 ± 11) 117	13 6 (11 ± 4) 14	38 33 (31 ± 8) 22	22 28 (23 ± 5) 18	11 11 (11 ± 0) 11
	313	91 116 (105 ± 13) 108	4 8 (10 ± 7) 18	21 25 (22 ± 3) 19	23 15 (20 ± 4) 21	11 10 (9 ± 3) 6
	625	120 103 (117 ± 13) 128	7 12 (10 ± 3) 12	27 16 (20 ± 6) 16	27 16 (27 ± 11) 38	7 13 (9 ± 3) 7
	1250	91 115 (104 ± 12) 107	15 15 (15 ± 0) 15	20 29 (25 ± 5) 25	23 36 (27 ± 8) 22	6 10 (8 ± 2) 8
	2500	116 102 (112 ± 8) 117	14 15 (13 ± 2) 11	21 26 (22 ± 4) 19	25 31 (29 ± 3) 30	11 13 (13 ± 2) 14
	5000	77 99 (93 ± 14) 102	11 12 (12 ± 1) 13	22 22 (22 ± 1) 23	19 22 (20 ± 2) 19	10 10 (10 ± 1) 11
+S9 mix	Negative control	139 145 (135 ± 12) 122	6 12 (10 ± 3) 11	34 34 (38 ± 6) 45	41 48 (42 ± 6) 37	20 22 (20 ± 2) 18
	313	135 116 (124 ± 10) 122	10 10 (10 ± 0) 10	28 19 (26 ± 6) 30	20 33 (32 ± 11) 42	19 13 (18 ± 4) 21
	625	110 108 (112 ± 5) 118	13 13 (13 ± 0) 13	27 42 (34 ± 8) 34	30 33 (32 ± 2) 34	11 11 (12 ± 2) 15
	1250	129 120 (126 ± 5) 129	11 8 (8 ± 3) 6	20 34 (24 ± 8) 19	35 16 (27 ± 10) 30	13 18 (18 ± 5) 22
	2500	111 117 (114 ± 3) 114	7 6 (8 ± 3) 11	23 28 (28 ± 5) 33	26 30 (27 ± 2) 26	13 19 (15 ± 3) 14
	5000	138 124 (120 ± 20) 98	12 10 (11 ± 1) 11	18 26 (25 ± 7) 31	45 25 (31 ± 12) 23	20 16 (18 ± 2) 18
Positive control -S9 mix	Chemical	AF-2	NaN_3	AF-2	AF-2	ICR-191
	Dose(μg/plate)	0.01	0.5	0.01	0.1	0.5
	Number of revertant colonies/plate	646 701 (656 ± 41) 622	430 409 (426 ± 15) 439	420 372 (390 ± 26) 377	397 401 (430 ± 53) 491	1369 1461 (1417 ± 46) 1422
Positive control +S9 mix	Chemical	2AA	2AA	2AA	2AA	2AA
	Dose(μg/plate)	1	2	10	0.5	2
	Number of revertant colonies/plate	825 852 (869 ± 55) 931	221 274 (253 ± 28) 265	677 681 (684 ± 8) 693	246 225 (249 ± 26) 276	313 294 (284 ± 36) 244

[Note]
- ( ): The mean number of colonies per plate.
- AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
- NaN_3: Sodium azide
- ICR-191: 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine·2HCl
- 2AA: 2-Aminoanthracene

Table 3 Results of the main test-2

Test substance:

Test Period		From September 12, 2008 to September 16, 2008				
With(+)or without(-) S9 mix	Test substance dose (μg/plate)	Number of revertant colonies per plate				
		Base-pair substitution type			Frameshift type	
		TA100	TA1535	WP2*uvrA*	TA98	TA1537
−S9 mix	Negative control	133 121 (118 ± 16) 101	8 14 (12 ± 3) 13	26 30 (30 ± 5) 35	37 30 (29 ± 8) 21	5 10 (7 ± 3) 7
	313	127 122 (117 ± 13) 102	15 7 (12 ± 5) 15	22 26 (23 ± 3) 20	12 21 (16 ± 5) 16	8 5 (6 ± 2) 5
	625	115 110 (118 ± 10) 129	6 11 (9 ± 3) 10	27 23 (25 ± 2) 26	15 27 (21 ± 6) 21	5 8 (6 ± 2) 5
	1250	103 107 (107 ± 5) 112	13 14 (12 ± 3) 8	35 29 (33 ± 3) 34	23 19 (21 ± 2) 21	7 5 (8 ± 3) 11
	2500	111 123 (116 ± 6) 115	12 5 (7 ± 4) 4	22 30 (27 ± 5) 30	25 22 (22 ± 3) 20	5 7 (5 ± 2) 3
	5000	118 115 (125 ± 14) 141	13 4 (10 ± 5) 12	23 29 (28 ± 5) 33	27 26 (22 ± 7) 14	6 7 (6 ± 2) 4
+S9 mix	Negative control	121 105 (116 ± 10) 123	14 10 (12 ± 2) 11	37 31 (32 ± 5) 27	20 26 (23 ± 3) 22	21 12 (18 ± 5) 21
	313	94 132 (120 ± 23) 135	10 11 (12 ± 2) 14	28 35 (29 ± 6) 23	33 20 (25 ± 7) 23	14 15 (14 ± 2) 12
	625	128 120 (129 ± 10) 139	15 10 (13 ± 3) 15	30 20 (25 ± 5) 25	21 22 (25 ± 6) 31	15 18 (15 ± 4) 11
	1250	129 120 (119 ± 11) 108	11 7 (9 ± 2) 8	21 19 (23 ± 5) 29	31 22 (28 ± 5) 30	19 10 (12 ± 6) 7
	2500	115 117 (120 ± 8) 129	5 7 (7 ± 2) 8	25 31 (27 ± 3) 25	26 26 (26 ± 0) 26	12 13 (14 ± 3) 18
	5000	146 128 (131 ± 13) 120	10 6 (7 ± 3) 4	34 31 (33 ± 2) 35	31 21 (26 ± 5) 25	13 12 (12 ± 2) 10
Positive control -S9 mix	Chemical	AF-2	NaN_3	AF-2	AF-2	ICR-191
	Dose(μg/plate)	0.01	0.5	0.01	0.1	0.5
	Number of revertant colonies/plate	859 880 (826 ± 76) 740	390 372 (393 ± 23) 418	414 415 (414 ± 1) 414	478 447 (478 ± 31) 509	1381 1427 (1395 ± 28) 1377
Positive control +S9 mix	Chemical	2AA	2AA	2AA	2AA	2AA
	Dose(μg/plate)	1	2	10	0.5	2
	Number of revertant colonies/plate	923 947 (919 ± 30) 887	241 236 (234 ± 9) 224	577 609 (571 ± 41) 527	332 309 (327 ± 17) 341	289 224 (244 ± 39) 218

[Note]
- ( ): The mean number of colonies per plate.
- AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
- NaN_3: Sodium azide
- ICR-191: 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine·2HCl
- 2AA: 2-Aminoanthracene

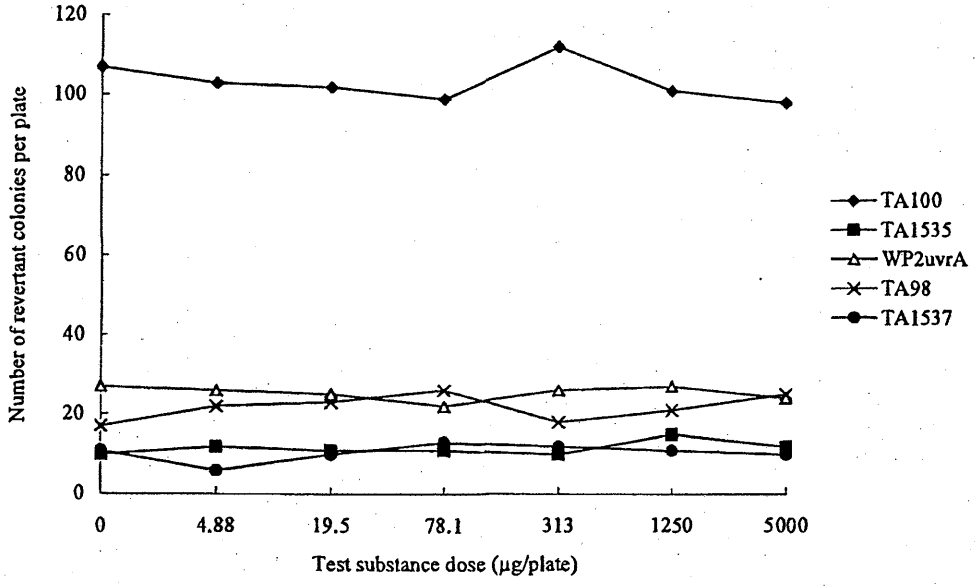


Fig. 1 Dose-response curve without S9 mix in the dose finding test

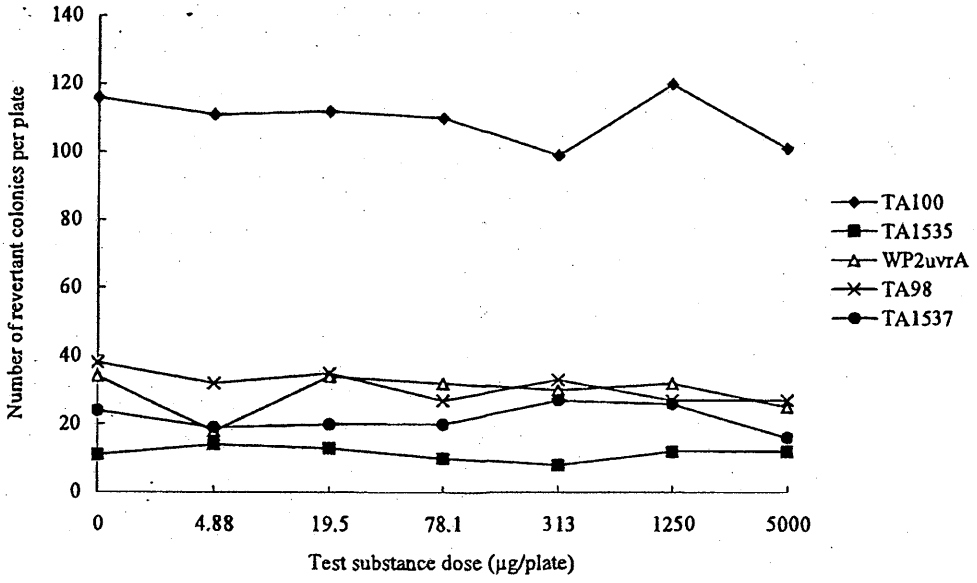


Fig. 2 Dose-response curve with S9 mix in the dose finding test

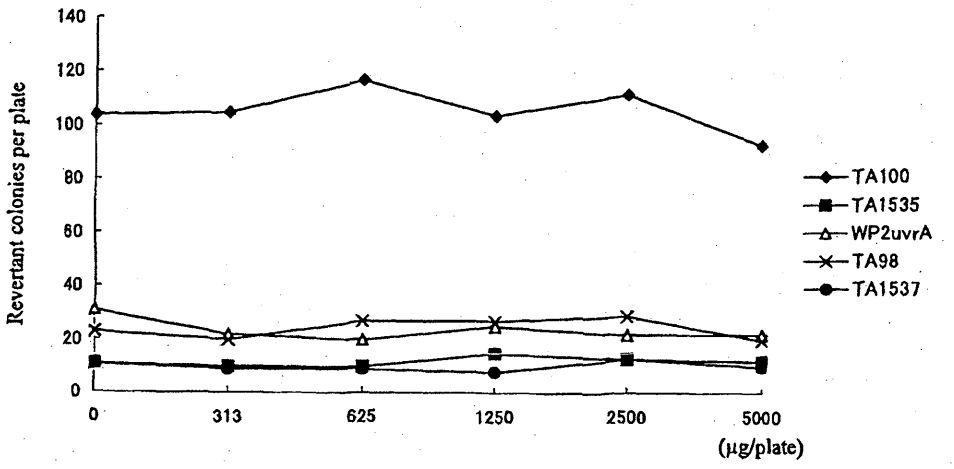


Fig. 3 Dose-response curve without S9 mix in the main test-1

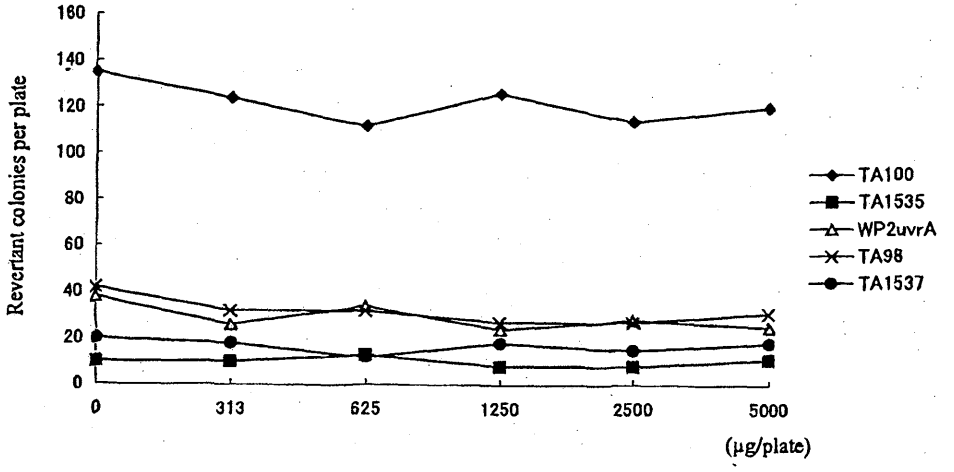


Fig. 4 Dose-response curve with S9 mix in the main test-1

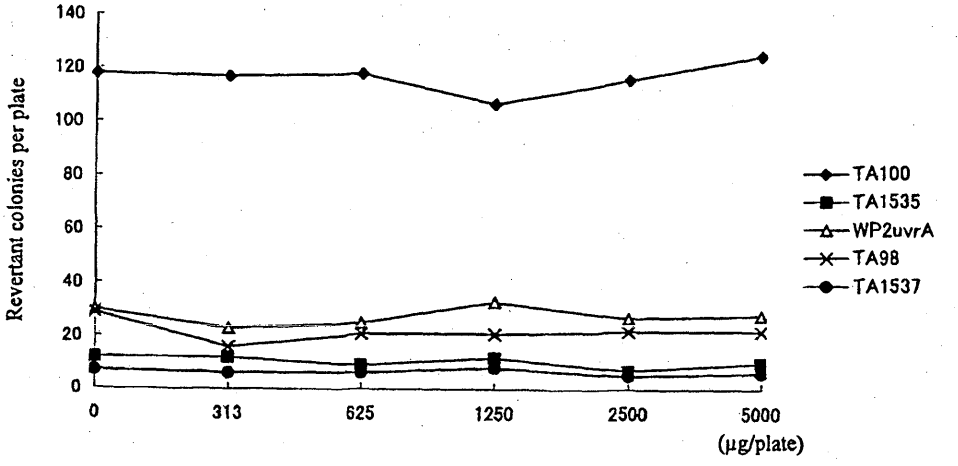


Fig. 5 Dose-response curve without S9 mix in the main test-2

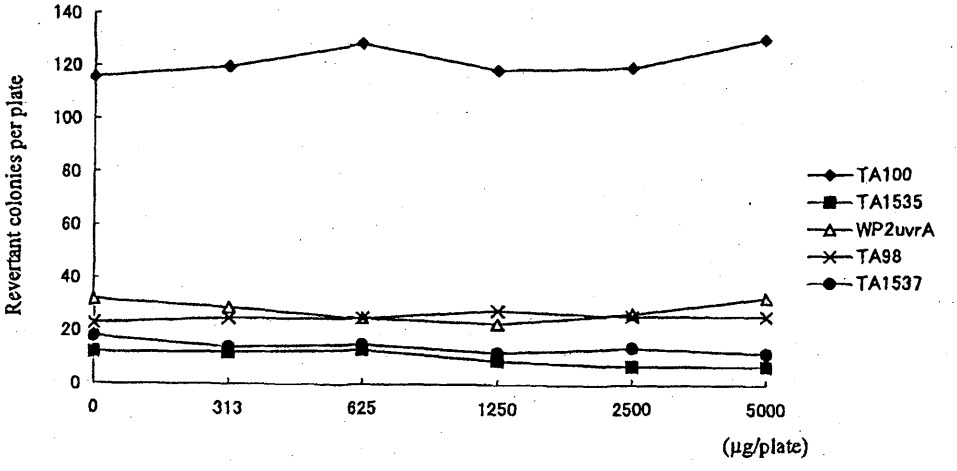


Fig. 6 Dose-response curve with S9 mix in the main test-2

HISTORICAL DATA
(Tesmedia AN)

February, 2008 -July, 2008

Negative Control(Mean±3S.D.)

	-S9 mix					+S9 mix				
	TA100	TA1535	WP2*uvrA*	TA98	TA1537	TA100	TA1535	WP2*uvrA*	TA98	TA1537
Mean	113	12	27	23	10	121	10	31	33	26
S.D.	16	4	8	5	4	17	4	9	7	8
Upper Limit	161	24	51	38	22	172	22	58	54	50
Lower Limit	65	1	3	8	1	70	1	4	12	2

Positive Control(Mean±3S.D.)

	-S9 mix					+S9 mix				
	TA100	TA1535	WP2*uvrA*	TA98	TA1537	TA100	TA1535	WP2*uvrA*	TA98	TA1537
Chemical	AF-2	NaN_3	AF-2	AF-2	ICR-191	2AA	2AA	2AA	2AA	2AA
Dose (μg/plate)	0.01	0.5	0.01	0.1	0.5	1	2	10	0.5	2
Mean	683	465	357	530	1765	912	241	638	298	247
S.D.	95	64	67	89	311	112	29	127	37	37
Upper Limit	968	657	558	797	2698	1248	328	1019	409	358
Lower Limit	398	273	156	263	832	576	154	257	187	136

[Notes]
- AF-2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
- NaN_3: Sodium azide
- ICR-191: 2-Methoxy-6-chloro-9-[3-(2-chloroethyl)-aminopropylamino]acridine·2HCl
- 2AA: 2-Aminoanthracene

ATTACHMENT HEADER SHEET

Attachment Number 009

Attachment Name

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study ...

Associated PMN Section Number

N/A

Does not contain CBI

Report Number

TSB2101224041049680

CERI

Receipt No. 827-08-D-3365

STUDY CODE: B11-0897

FINAL REPORT

TWENTY-EIGHT-DAY REPEATED-DOSE ORAL TOXICITY STUDY OF [redacted] IN RATS

January 2009

Hita Laboratory
Chemicals Evaluation and Research Institute
Japan

ALL CIRCLED INFORMATION IS CONFIDENTIAL

STATEMENT

I, the undersigned, hereby declare that this report provides correct English translation of the final report (Study Code B11-0897, issued on January 9, 2009).

Katsumi Miyata

July 2, 2009

Katsumi Miyata, M.S., J.A.C.L.C.T.
Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

Date

GLP STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Title: Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of in Rats

Study Code: B11-0897

I, the undersigned, hereby declare that this study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (2003.11.17) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)".

And, I confirmed that this report accurately reflects the raw data obtained and that data of the study has reliability.

Study Director: Signed in original January 9, 2009

Katsumi Miyata, M.S., J.A.C.L.C.T.

QUALITY ASSURANCE STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Title: Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of in Rats

Study Code: B11-0897

This study was audited and inspected by Quality Assurance Section of Hita Laboratory, Chemicals Evaluation and Research Institute, Japan. The dates audited and/or inspected and the dates reported of these results to the study director and management are as follows.

Items of Inspections and Audits	Dates of Inspections and Audits	Dates of Inspections and Audits Reports
Protocol	September 1, 2008	September 1, 2008
Preparation of test substance	September 5, 2008	September 5, 2008
Allocation and animal identification	September 8, 2008	September 8, 2008
Food intake measurements	September 8, 2008	September 8, 2008
Administration and clinical observation	September 9, 2008	September 9, 2008
Amendment to protocol	September 12, 2008	September 12, 2008
Urine sampling	October 6, 2008	October 6, 2008
Blood sampling	October 7, 2008	October 7, 2008
Trimming, autopsy and organ weight measurements	October 7, 2008	October 7, 2008
Hematology	October 7, 2008	October 7, 2008
Urinalysis	October 7, 2008	October 7, 2008
Blood chemistry	October 8, 2008	October 8, 2008
Pathological preparation	October 17, 21 and 29, 2008	October 29, 2008
Clinical chemistry data	December 22, 2008	December 22, 2008
Pathological data	December 22, 2008	December 22, 2008
Detailed clinical observation and sensorimotor function	December 22, 2008	December 22, 2008
Animal data	December 24, 2008	December 24, 2008
Documents of test substance and housing conditions	December 24, 2008	December 24, 2008
Re-inspection of animal data	December 26, 2008	December 26, 2008
Re-inspection of documents of test substance and housing conditions	December 26, 2008	December 26, 2008
Draft of final report	January 5, 2009	January 5, 2009
Re-inspection of draft final report	January 6, 2009	January 6, 2009
Draft of final report (2nd)	January 7, 2009	January 7, 2009
Re-inspection of draft final report (2nd)	January 8, 2009	January 8, 2009
Final report	January 9, 2009	January 9, 2009

Following items were reported to the study director and management on the basis of the audit of facility or audit results in other study.

Items of Audits	Dates of Audits	Dates of Audits Reports
Preparation investigation	June 4, 2008	January 9, 2009
Animal receipt	July 8, 2008	January 9, 2009
Quarantine and acclimatization	July 7, 2008	January 9, 2009
Animal care	July 8, 2008	January 9, 2009
Body weight measurements	July 8, 2008	January 9, 2009
Detailed clinical observation and sensorimotor function	July 1, 2008	January 9, 2009
Microscopic examinations	October 20, 2008	January 9, 2009

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study and that the reported results accurately reflect the raw data obtained.

Section Chief, Quality Assurance: Signed in original January 9, 2009

Ryuichiro Mizuguchi, B.S.

TABLE OF CONTENTS

Study Code: B11-0897
Test Substance Code: HR7578
Sponsor Code: I-0010

TITLE

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of in Rats

SPONSOR

TESTING FACILITY

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan
822, 3-chome, Ishii-machi, Hita, Oita 877-0061, Japan

PURPOSE OF THE STUDY

The purpose of this study is to define the type, severity and reversibility of toxicological signs of the test substance by observing the functional and morphological changes in animals receiving repeated doses orally for 28 days.

TESTING METHOD

This study was conducted in accordance with "28-day Repeated Dose Toxicity Study in Mammalian Species" prescribed in "Concerning Testing Methods Relating to the New Chemical Substances" (Notification No. 1121002 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 2 (2003.11.13) of the Manufacturing Industries Bureau, METI & No. 031121002 of the Environmental Health Department, MOE (November 21, 2003)".

GLP COMPLIANCE

This study was conducted in conformity "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (2003.11.17) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)".

PERIOD OF THE STUDY

Commencement of the Study:	August 28, 2008
Animal Receipt:	September 2, 2008
Initiation of Examination (Initiation of Dosing):	September 9, 2008
Terminal Necropsy of Dosing Period:	October 7, 2008
Initiation of Recovery Period:	October 7, 2008
Terminal Necropsy of Recovery Period:	October 21, 2008
Termination of Examination (Termination of Histology):	December 4, 2008
Completion of the Study:	January 9, 2009

LOCATION AND PERIOD FOR RETENTION OF RAW DATA AND SPECIMENS

The raw data, protocol and amendment, study contract documents, test substance information, final report, other record documents and specimens will be stored in the archive of the Hita Laboratory of our organization, and samples of every lot of the test substance in the test substance storage room, for a period of 10 years from the date of receipt of the notification that they are applicable to Article 4, Paragraphs 1 or 2, Article 4-2, Paragraphs 2, 3 or 8, Article 5-4, Paragraph 2, Article 24, Paragraph 2 or Article 25-3, Paragraph 2 of the Japanese Chemical Substances Control Law No. 117 (1973). The sponsor will inform the Hita Laboratory of our organization of the date of receipt of the notification. After termination of the retention period, any measures taken will be done so with the approval of the sponsor. Samples and specimens that are liable to deteriorate markedly will be retained for 10 years after receipt of the notification or only for as long as the quality of the preparation permits evaluation with the sponsor's consent.

RETENTION OF THE ORIGINAL PROTOCOL AND FINAL REPORT

The original protocol and final report will be retained at Hita Laboratories. A copy of the document will be retained by the sponsor.

AUTHOR AND PERSONNEL CONCERNED WITH THE STUDY

Study Director: Katsumi Miyata, M.S., J.A.C.L.C.T.
(Planning and management of the study, evaluation of the results, report creation, and over all responsible for the technical conduct of the study)

Study Staff: Saori Takakura, J.L.A.T., J.A.C.L.C.T.
(Quarantine, acclimation and housing management of animals, preparation and administration of the test substance, clinical observation, detailed clinical observation, sensorimotor function, body weights and food intakes measurements, and responsible for the animal examination)

Person in charge of Pathologic Examination:
Satsuki Houshuyama, Ph.D., D.V.M.
(Necropsy, collection of tissues, organ weight measurements, histopathological examinations, and responsible for the histopathology)

Person in charge of Clinical Chemistry:
Nobuhiko Higasihara, B.S.
(Hematological and blood chemical examinations, urinalysis, and responsible for the biochemistry of the specimens)

AUTHOR APPROVAL

Study Director: Signed in original January 9, 2009
Katsumi Miyata, M.S., J.A.C.L.C.T.
General Toxicology Section
Hita Laboratory

SUMMARY

A 28-day repeated oral dose toxicity study of was performed in groups of five male and five female Crl:CD(SD) rats at 5 weeks of age. The high dose was set at 1,000 mg/kg/day, and altogether three doses including 250 and 50 mg/kg/day were employed. Recovery groups were also set for the 1,000 mg/kg and vehicle control groups to investigate the reversibility of the effects.

Effects of the test substance were not observed in the clinical observation, detailed clinical observation, sensorimotor function, body weight, food consumption, blood chemistry, urinalysis, organ weight, necropsy and histopathological examination.

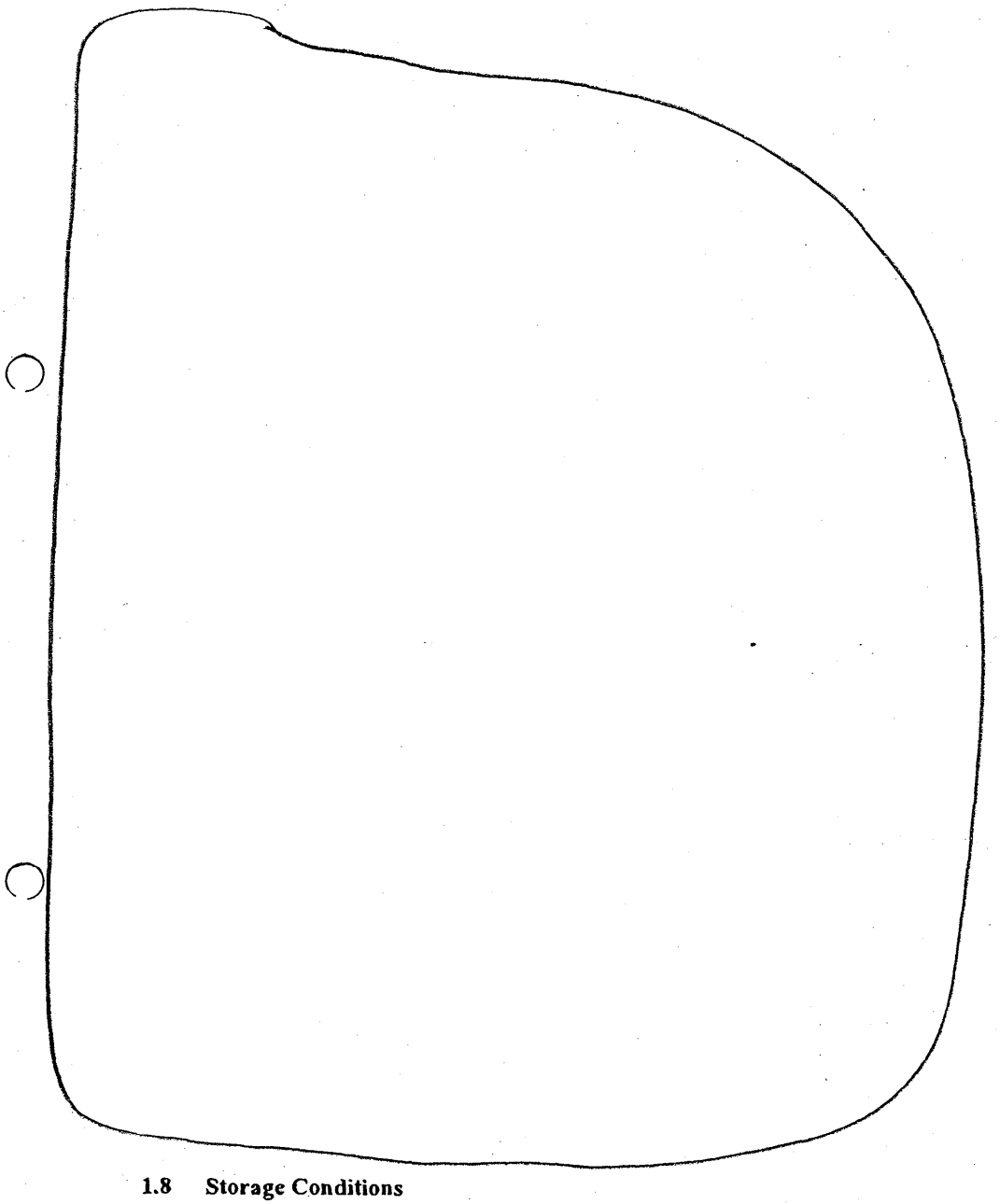
In the hematology, decreased hemoglobin conc. and increased reticulocyte count were noted in females of the 1,000 mg/kg group.

The NOAEL of was considered to be 1,000 mg/kg/day under the conditions tested.

The NOEL was considered to be 250 mg/kg/day due to decreased hemoglobin conc. and increased reticulocyte count without abnormal RBC

MATERIALS AND METHODS

1. TEST SUBSTANCE (Information provided by the sponsor)



1.8 Storage Conditions

The sealed test substance was stored at room temperature (20.5-22.8°C from obtaining of the test substance to the final preparation of the dosing formulations) in the test substance storage room.

1.9 Handling Precaution

Glove, mask, cap, protective glasses and lab coat were put on.

2. ANIMALS

Crl:CD(SD) rats (SPF) of thirty three males and thirty three females were obtained from Charles River Japan Hino Breeding Center at four weeks old. Animals were acclimatized for 7 days including 6 days quarantine. No abnormalities were noted in all animals during the quarantine and acclimation periods. The animals were allocated to groups to ensure homogeneity of mean body weights using body weight-stratified randomization on one day before the start of the administration. The animals not treated were excreted from the study and euthanized under ether anesthesia. At the onset of the treatment, the animals were 5 weeks old with body weight ranges of 121.3-145.8 g and 105.3-123.2 g for males and females, respectively.

Animals were identified by means of a marker on the tail before grouping and ear-tags after grouping. However the detailed clinical examination, reflex and grip strength measurement were performed ad blind tests. The racks and cages were identified by individual cards.

3. HOUSING CONDITIONS

The barrier-system animal room was maintained at a stable temperature (21-25°C) and relative humidity (40-70%) with 10-15 air changes per hour and artificial light-dark cycle of 12-12 hours (light on: 7:00 and light off: 19:00). The actual temperature and humidity were 21.8-23.8°C and 48.1-68.4%, respectively.

The rats were housed in hanging stainless steel cages with wire-mesh floor at three or five animals/cage (260 W×380 D×180 H mm, TOKIWA KAGAKU KIKAI) for quarantine and acclimation, and at one animal/cage (165 W×300 D×150 H mm, TOKIWA KAGAKU KIKAI) for after grouping.

Under trays were changed once before grouping, and twice weekly after grouping. Feeders, cages and racks were changed once at the grouping, and once at the termination of the dosing period for the recovery group.

The animals had free access to an MF pelleted diet (Lot No. 080318 and 080716, Oriental Yeast) and chlorinated water from the Hita City supply via automatic watering system with sipper tubes. The diet and housing materials were autoclaved at 121°C for 30 min prior to use. Analysis of the diet was performed in Japan Food Research laboratories, and the analytical data were provided by the manufacturer. The tested parameters met the

requirements in our laboratories according to the "Toxic Substances Control Act of US-EPA". Contaminants in drinking water were analyzed twice a year in Oita Prefecture Pharmaceutical Association according to the water regulations of the "Notification No. 101 of Environmental Health Bureau, MHW" except for the taste and residual chlorine. Contaminants in the water were in the stated ranges in our laboratory.

4. GROUPING

Range finding study of 7 days repeated oral treatment was performed at 0, 25, 250, 500 and 1,000 mg/kg/day. No abnormalities were noted in all dose groups. Accordingly, the high dose was set at 1,000 mg/kg/day and lower doses of 250 and 50 mg/kg were set for the present study. A further group of five males and five females were set for the recovery groups to investigate the reversibility of the effects.

Group	Dose (mg/kg/day)	Volume (mL/kg)	Concentration (w/v%)	No. of Animals (Animal No.) Male	Female
Vehicle control	0	10	0	5 (1 - 5)	5 (31 - 35)
Vehicle control (recovery)	0	10	0	5 (6 - 10)	5 (36 - 40)
Low dose	50	10	0.5	5 (11 - 15)	5 (41 - 45)
Intermediate dose	250	10	2.5	5 (16 - 20)	5 (46 - 50)
High dose	1,000	10	10.0	5 (21 - 25)	5 (51 - 55)
High dose (recovery)	1,000	10	10.0	5 (26 - 30)	5 (56 - 60)

5. STABILITY OF THE TEST SUBSTANCE (see attached X-ray diffraction report)

Stability of the test substance during the dosing period was confirmed in Tokyo laboratory under non-GLP. X-ray diffractometer was used to confirm the stability with the test substance from Kurume laboratory before dosing period and with that from Hita laboratory after the dosing period. There were no changes between X-ray diffraction spectra provided by the sponsor and before dosing period, and also after the dosing period. Therefore the test substance was confirmed to be stable during the dosing period.

6. PREPARATION OF FORMULATIONS

6.1 Vehicle

In preparation investigation of the dosing formulations, although the test substance did not dissolved in purified water, the suspended state was good. Therefore, purified water (Lot No. 080613A, Takasugi Pharmaceutical) was selected as the vehicle.

6.2 Preparation and Storage

The test substance was accurately weighed and mixed with purified water to prepare 10.0 w/v%. The lower concentrations of 0.5 and 2.5 w/v% were diluted from 10.0 w/v% with purified water, stirring with a magnetic stirrer. The formulations including purified water for the vehicle control were stored at the dark and cold place (2-10°C, refrigerator No. 7 in the test substance preparation room).

Date	Concentration (w/v%)	Test substance weights and dilution methods	Volume (mL)
September 5, 2008	10.0	20.00 g	200
(Concentration	2.5	Diluted with 25 mL of 10.0 w/v%	100
conformation)	0.5	Diluted with 5 mL of 10.0 w/v%	100
September 10, 2008	10.0	50.00 g	500
	2.5	Diluted with 75 mL of 10.0 w/v%	300
	0.5	Diluted with 15 mL of 10.0 w/v%	300
September 19, 2008	10.0	80.00 g	800
	2.5	Diluted with 100 mL of 10.0 w/v%	400
	0.5	Diluted with 20 mL of 10.0 w/v%	400
September 29, 2008	10.0	70.00 g	700
	2.5	Diluted with 75 mL of 10.0 w/v%	300
	0.5	Diluted with 15 mL of 10.0 w/v%	300

6.3 Homogeneity and Stability Tests (see attached physicochemical report)

The homogeneity and stability tests were performed in Hita Laboratory. In the homogeneity test, top, middle and bottom layers of 10.0 and 0.5 w/v% formulations were taken just after preparation. Each sample was weighed after drying. In the stability test, the homogeneity samples were stored at the dark and cold place and analyzed after 7 and 12 days. The test substance in formulations was confirmed to be stable for 11 days.

6.4 Concentration Conformation

Concentration of the test substance was confirmed in Hita Laboratory. The concentrations of 10.0, 2.5 and 0.5 w/v% formulations were confirmed to be within 100±10% of each nominal concentration at the first preparation of the dosing period.

7. ADMINISTRATION

The formulations were mixed with a magnetic stirrer and repeatedly administered daily in the morning (8:30-11:15) by oral gavage using a syringe (Terumo) connected to a Nelaton catheter (Terumo) for 28 days. Thereafter, a 14-day recovery period was set.

8. OBSERVATIONS

8.1 Clinical Signs

During the dosing period, animals were observed three times a day, i.e., before dosing (in the morning), during and just after dosing, and in the afternoon, daily from day 1 to day 28. During the recovery period, animals were observed once daily.

8.2 Detailed Clinical Observations

The detailed examination in all animals was performed ad blind tests before dosing and once weekly thereafter.

1) Removal from cage

The case with which the animal was removed from the home cage was recorded.

Ease of removal and vocalization.

2) Handling observations

In hand observations

Muscle tone, subnormal temperature, piloerection, hair appearance (staining and unkempt hair), skin color and mucous (paleness, reddening and cyanosis), eyes (lacrimation, exophthalmos and pupillary size), salivation and secretion.

3) Observation in arena

Animals were placed in the standard arena and observed, and number of defecation and urination were recorded for 1 min.

Posture, motor activity level, respiration, lid closure, gait characteristics, tremor, twitch, convulsion, stereotypes and abnormal behavior.

8.3 Sensorimotor Function

All animals were examined in week 4. Locomotor activity counts were measured in females of the vehicle and 1,000 mg/kg recovery groups in recovery week 2, since a statistically significant difference was noted in females of the 1,000 mg/kg group during the dosing period.

1) Reflex

Sensory reactivity to stimuli of different types was performed ad blind tests.

(1) Approach contact/touch response

A blunt probe was bought approximately 3 cm from the animal's nose for 4 seconds.

(2) Pinna response

The animal's response to a sudden sound of finger snap was assessed.

(3) Pain response

The animal's tail was pinched with a clothespin between one-third and base of the tail.

(4) Pupillary reflex

Following darkness adaptation of the animal's eyes, pupil constriction in response to a bright beam of light was observed.

(5) Air righting reflex

The animal was held ventral surface uppermost approximately 30 cm height from the flat surface and released.

2) Grip strength

Forelimbs and hindlimbs grip strengths were measured with automated grip strength meter (FGC-2, MATYS) ad blind tests. Two trials were performed, and the mean values were calculated.

3) Locomotor activity counts

Locomotor activity level of each animal was counted with activity monitoring system for rats (ACTIMO-10, SHINTECHNO) by the number of crossing IR beam for 1 hour at 10 min intervals.

8.4 Body Weights

Body weight was measured at allocation to groups, and on days 1, 3, 8, 12, 17, 21, 26 and 28 during the dosing period and on days 1, 5, 10 and 14 (recovery) during the recovery period. In addition, immediately before necropsy, body weights were measured for calculation of the relative organ weights.

8.5 Food Intakes

Food consumption was measured at allocation to groups, and on days 1, 3, 8, 15, 22 and 28 during the dosing period and on days 1, 4, 8 and 14 during the recovery period.

8.6 Hematological Examinations

Blood or plasma samples obtained by blood sampling from the abdominal aorta under ether anesthesia after overnight fasting (16 to 20 hr) at the completion of the dosing period (excluding the recovery groups) and at the completion of the recovery period were determined for the following items.

As an anticoagulant, 3.2% sodium citrate aqueous solution (Lot No. PEQ4430, Wako Pure Chemical Industries) was used for the determination of prothrombin time and activated partial thromboplastin time, and EDTA-2K (Lot No. G7039, Sysmex) for other measurements.

	Parameters		Method
1)	Red blood cell count (RBC)	($\times 10^4/\mu L$)	Electrical resistance detection
2)	White blood cell count (WBC)	($\times 10^2/\mu L$)	Electrical resistance detection
3)	Hemoglobin conc. (Hb)	(g/dL)	Noncyanhemoglobin method
4)	Hematocrit value (Ht)	(%)	$\frac{RBC \times MCV}{10^3}$
5)	Mean corpuscular volume (MCV)	(fL)	Electrical resistance detection
6)	Mean corpuscular hemoglobin (MCH)	(pg)	$\frac{Hb}{RBC} \times 10^3$
7)	Mean corpuscular hemoglobin conc. (MCHC)	(g/dL)	$\frac{Hb}{Ht} \times 10^2$
8)	Platelet count (Platelet)	($\times 10^4/\mu L$)	Electrical resistance detection
9)	Reticulocyte count (Reticulo)	(%)	RNA staining
10)	Prothrombin time (PT)	(sec)	Magnetic sensor
11)	Activated partial thromboplastin time (APTT)	(sec)	Magnetic sensor
12)	Differentiation of leukocytes	(%)	Flow cytometry technique
	Neutrophils (Neutro)		
	Eosinophils (Eosino)		
	Basophils (Baso)		
	Lymphocytes (Lymph)		
	Monocytes (Mono)		
	Large unstained cells (LUC)		

1) - 8) CELL-DYN3500, Abbott Laboratories

9), 12) ADVIA 120, SIEMENS

10), 11) KC-10A, AMELUNG

8.7 Blood Chemical Examinations

Serum samples were separated from blood samples collected at the same times as those described in section 8.6, and the following items were determined in the obtained serum samples.

	Parameters		Method
1)	Aspartate aminotransferase (AST)	(IU/L)	UV method (method based on JSCC)
2)	Alanine aminotransferase (ALT)	(IU/L)	UV method (method based on JSCC)
3)	Alkaline phosphatase (ALP)	(IU/L)	*p*-Nitrophenyl phosphate method
4)	Cholinesterase (ChE)	(IU/L)	Butyrylthiocholine iodide method
5)	γ-Glutamyl transpeptidase (γ-GTP)	(IU/L)	L-γ-glutamyl-3-carboxy-4-nitroanilide method
6)	Total cholesterol (T-Cho)	(mg/dL)	COD·ADPS method
7)	Triglyceride (TG)	(mg/dL)	GPO·ADPS glycerol blocking method
8)	Glucose	(mg/dL)	Hexokinase·G-6-PDH method
9)	Total protein (T-Protein)	(g/dL)	Biuret method
10)	Albumin	(g/dL)	Bromocresol green method
11)	A/G ratio		$\frac{\text{Albumin}}{\text{T-Protein}-\text{Albumin}}$
12)	Blood urea nitrogen (BUN)	(mg/dL)	Urease·GlDH method
13)	Creatinine	(mg/dL)	Creatininase·F-DAOS method
14)	Total bilirubin (T-Bil)	(mg/dL)	Enzyme method
15)	Calcium (Ca)	(mg/dL)	OCPC method
16)	Inorganic phosphorus (IP)	(mg/dL)	Fiske-Subbarow method
17)	Sodium (Na)	(mEq/L)	Crown-Ether membrane electrode method
18)	Potassium (K)	(mEq/L)	Crown-Ether membrane electrode method
19)	Chloride (Cl)	(mEq/L)	Coulometric titration method

1)-10), 12)-16) 7170 Automatic Analyzer, Hitachi

17)-19) PVA-EXII, A & T

8.8 Urinalyses

Urinalysis was performed once (day 28) during the dosing period (excluding the recovery groups) and once (day 14) during the recovery period. Urine samples (accumulated for 15-17 hr) collected in individual metabolic cages (150 W×200 D×263 H mm) were determined with drinking water ad lib. The urine sediments was stained and examined in males and females of the vehicle control and 1,000 mg/kg groups at the end of the dosing period.

	Parameters		Method
1)	Urine volume	(m/L)	Volumetric method
2)	Color		Macroscopy
3)	Turbidity		Macroscopy
4)	Urine osmotic pressure (Uosm)	(mOsm/L)	Freezing-point depression method
5)	pH		Test paper
6)	Protein		Test paper
7)	Glucose		Test paper
8)	Occult blood		Test paper
9)	Urinary sediments		Sternheimer

4) OM-6040, ARKRAY

5)-8) Hema-Combistix, SIEMENS

9) Biological microscope, BX41, OLYMPUS

8.9 Pathological Examinations

1) Necropsy

All animals were subjected to the detailed gross necropsy including body surface, all orifices, cranial, subcutis, thoracic, abdominal and pelvic cavities, and the contents.

2) Organ weights

Weights of the following organs were measured in all animals. The relative organ weight was also calculated based on the body weight at the time of necropsy.

Liver, heart, kidneys, testes, epididymides, ovaries, brain, spleen, thymus and adrenals

3) Histopathological examinations

(1) The following organs and tissues were taken. Trachea, lungs and urinary bladder were filled with 10% neutralized buffered formalin before taken. Stomach and intestines were filled and fixed with 10% neutralized buffered formalin and were wash with water. All organs/tissues were preserved in 10% neutralized buffered formalin. However, testes and epididymides were fixed in Bouin's solution.

Category	Organs and Tissues
Respiratory system	Trachea, lungs
Digestive system	Stomach, intestine (duodenum to rectum, with Peyer's patches), liver
Cardiovascular system	Heart
Urinary system	Kidneys, urinary bladder

Reproductive system	Testes, epididymides, prostate, seminal vesicle, ovaries, uterus, vagina
Nervous system	Brain (cerebrum, cerebellum and pons), spinal cord, sciatic nerve
Hematopoietic and lymphatic systems	Bone marrow (femur), axillar and mesenteric lymph nodes, spleen, thymus
Endocrine system	Pituitary gland, thyroids (with parathyroids), adrenals
Special sense organ	Eye balls

(2) Skin was taken as a macroscopic region in one animal (No. 19) of the 250 mg/kg group.

(3) Light microscopic examinations were performed for the organs and tissues of the following groups after embedding in paraffin, sectioning and hematoxylin and eosin (HE) staining. Decalcification was done for bone marrow (femur) with 10% formic acid formalin before cutting. "♂/♀" show groups which were examined and "-" shows examinations were not done.

Organ・tissue	Vehicle control group	Vehicle control recovery group	25 mg/kg group	250 mg/kg group	1,000 mg/kg group	1,000 mg/kg recovery group
Trachea	♂♀	-	-	-	♂♀	-
Lungs	♂♀	-	-	-	♂♀	-
Forestomach	♂♀	-	-	-	♂♀	-
Glandular stomach	♂♀	-	-	-	♂♀	-
Duodenum-ileum	♂♀	-	-	-	♂♀	-
Cecum- rectum	♂♀	-	-	-	♂♀	-
Liver	♂♀	-	-	-	♂♀	-
Heart	♂♀	-	-	-	♂♀	-
Kidneys	♂♀	-	-	-	♂♀	-
Urinary bladder	♂♀	-	-	-	♂♀	-
Testes	♂	-	-	-	♂	-
Epididymides	♂	-	-	-	♂	-
Prostate	♂	-	-	-	♂	-
Seminal vesicles	♂	-	-	-	♂	-
Ovaries	♀	-	-	-	♀	-
Uterus	♀	-	-	-	♀	-
Vagina	♀	-	-	-	♀	-

Cerebrum, cerebellum, pons	♂♀	-	-	-	♂♀	-
Spinal cord	♂♀	-	-	-	♂♀	-
Sciatic nerve	♂♀	-	-	-	♂♀	-
Bone marrow	♂♀	-	-	-	♂♀	-
Axillar lymph nodes	♂♀	-	-	-	♂♀	-
Mesenteric lymph nodes	♂♀	-	-	-	♂♀	-
Spleen*[1]	♂♀	♀	♀	♀	♂♀	♀
Thymus	♂♀	-	-	-	♂♀	-
Pituitary gland	♂♀	-	-	-	♂♀	-
Thyroids	♂♀	-	-	-	♂♀	-
Parathyroids	♂♀	-	-	-	♂♀	-
Adrenals	♂♀	-	-	-	♂♀	-
Eye balls	♂♀	-	-	-	♂♀	-

*1 Since change suspected to be effect of the test substance were noted in females of the 1,000 mg/kg group in the necropsy, histopathological examinations of spleen were done for all females including the recovery groups.

(4) Gross lesions in the glandular stomach (animal No. 9) and in the spleen (animal No. 10) in the vehicle control recovery group, and skin (animal No. 19) in the 250 mg/kg group were examined histopathologically.

9. STATISTICAL ANALYSIS

Data regarding body weights (excluding those at the time of necropsy), food intakes, hematological examinations, blood chemical examinations, urine volume, urine osmotic pressure, organ weights and FOB metrical data (grip strength and locomotor activity count) were analyzed using the Bartlett's test for homogeneity of variance. If the variances were homogeneous at a significance level of 5%, one way analysis of variance was performed. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment groups was analyzed by the Dunnett's test. If the variances were not homogeneous, the Kruskal-Wallis's test was used. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment group was analyzed by the nonparametric Dunnett's test.

FOB numerical data (defecation and urination) was analyzed using the Kruskal-Wallis's test. If there was a significant difference in this analysis, the difference between the vehicle control group and each of the treatment groups was analyzed by the nonparametric Dunnett's test.

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED THE RELIABILITY OF THE STUDY RESULTS

Although it was stated that stability of the test substance was confirmed between before and after the dosing period with X-ray diffraction spectra in the protocol, the spectrum measured before the dosing was also compared to the spectrum provided by the sponsor before dosing.

RESULTS

1. CLINICAL SIGNS (Table 1, Addendum 1)

1.1 During Dosing Period

In males, fur loss was observed in one animals of the 250 mg/kg group without dose relationship. No abnormalities were noted in the 50 or 1,000 mg/kg groups.

In females, no abnormal clinical signs were noted in all groups.

1.2 During Recovery Period

No abnormalities were noted in both sexes of the 1,000 mg/kg recovery groups.

2. DETAILED CLIUNICAL OBSERVATIONS (Table 2, Addendum 2)

2.1 During Dosing Period

No abnormalities were noted in all groups.

2.2 During Recovery Period

No abnormalities were noted in both sexes of the 1,000 mg/kg recovery groups.

3. SENSORIMOTOR FUNCTION (Tables 3, 4 and 5, Addenda 3, 4 and 5)

3.1 During Dosing Period

No abnormalities were noted in all males.

In females, locomotor activity counts were significantly decreased in 10-20 min in the 1,000 mg/kg group. No abnormalities were noted in the 50 or 250 mg/kg groups.

3.2 During Recovery Period

Males were not examined since no abnormalities were noted during the dosing period.

No abnormal locomotor activity counts were detected in females of the 1,000 mg/kg recovery group, although locomotor activity count was decreased during the dosing period.

4. BODY WEIGHTS (Fig.1, Table 6, Addendum 6)

4.1 During Dosing Period

No abnormal body weights were observed in males and females.

4.2 During Recovery Period

No abnormal body weights were noted in both sexes of the recovery groups.

5. FOOD INTAKES (Fig.2, Table 7, Addendum 7)

5.1 During Dosing Period

Food consumption was significantly increased in males of the 250 mg/kg group on day 28. However, this was not dose-related change. No abnormalities were noted in 50 and 1,000 mg/kg groups.

No abnormalities were noted in females of all groups.

5.2 During Recovery Period

No abnormalities were noted in males and females.

6. HEMATOLOGICAL EXAMINATIONS (Table 8, Addendum 8)

6.1 At Termination of Dosing Period

In males, MCHC was significantly decreased in the 250 mg/kg group with no dose-relationship. No abnormalities were noted in the 50 or 1,000 mg/kg groups.

6.2 At Termination of Recovery Period

No abnormalities were noted in both sexes.

7. BLOOD CHEMICAL EXAMINATIONS (Table 9, Addendum 9)

7.1 At Termination of Dosing Period

Potassium was significantly decreased in males of the 1,000 mg/kg group. In the 50 and 250 mg/kg group abnormal signs were not noted.

No abnormalities were noted in females of all groups.

7.2 At Termination of Recovery Period

No abnormalities were noted in both sexes.

8. URINALYSES (Table 10, Addendum 10)

8.1 At Termination of Dosing Period

No abnormalities were noted in males and females of all groups.

8.2 At Termination of Recovery Period

No abnormalities were noted in the 1,000 mg/kg recovery groups.

9. ORGAN WEIGHTS (Tables 11 and 12, Addenda 11 and 12)

9.1 At Termination of Dosing Period

In males, absolute adrenal weights were significantly increased in the 1,000 mg/kg group. In the 50 and 250 mg/kg group abnormal signs were not noted.

No abnormalities were noted in females.

9.2 At Termination of Recovery Period

No abnormalities were noted in the 1,000 mg/kg recovery groups.

10. NECROPSY (Table 13, Addendum 13)

10.1 At Termination of Dosing Period

In males, fur loss was observed in one animal of the 250 mg/kg group. Pelvic dilatation of the left kidney was observed in one animal of the 1,000 mg/kg group. No abnormal change was observed in the 50 mg/kg group.

In females, nodule in the spleen in one animal and decreased size of the left lobe in the thyroid

in another animal were observed in the 1,000 mg/kg group. No abnormalities were noted in the 50 or 250 mg/kg groups.

10.2 At Termination of Recovery Period

No abnormal sign was observed in males of the 1,000 mg/kg recovery group. Elevated region of the mucosa in the glandular stomach in one male and whitish region on the capsule of the spleen in one male were observed in the vehicle control recovery group.

No abnormalities were noted in females.

11. HISTOPATHOLOGICAL EXAMINATIONS (Table 14, Addendum 13)

11.1 At Termination of Dosing Period

In males, unilateral pelvic dilatation in the kidney was observed in one animal of the 1,000 mg/kg group. No abnormality was observed in the skin although fur loss was observed in the necropsy in the 250 mg/kg group. Histopathological examination was not performed for the 50 mg/kg group.

In females, microgranuloma in the liver and mineralization in the corticomedullary junction in the kidney were observed in one animal of the vehicle control group. Subcapsular cyst formation in the kidney and Rathke's pouch remnant in the pituitary gland were observed in another animal of the vehicle control group. Microgranuloma in the liver and ectopic thymus tissue in the thyroid were observed in one animal of the 1,000 mg/kg group. Hyperplasia of the lymphoid cells in the spleen in one animal and aplasia of the left lobe in the pituitary gland in one animal were observed in the 1,000 mg/kg group. No abnormal change was observed in the 50 or 250 mg/kg groups.

11.2 At Termination of Recovery Period

In males, histopathological examination was not performed for males of the 1,000 mg/kg recovery group. Squamous epithelial cyst in the glandular stomach in one animal and capsulitis in the spleen in another animal were observed in the vehicle control recovery group.

Although spleen was examined, no abnormal sings were noted in females of the 1,000 mg/kg recovery group.

DISCUSSION

The test substance did not affected to the clinical observation, detailed clinical observation, body weight, food intakes or urinalysis.

In the sensorimotor function, locomotor activity counts were decreased in females of the 1,000 mg/kg group in week 4 of the administration period. However, this was a single occurrence observed in 10-20 min and considered to be no treatment related since there were no abnormalities in the clinical observation and detailed clinical observation.

In the hematology, decreased hemoglobin conc. and increased reticulocyte count in females of the 1,000 mg/kg group were not considered to be toxicologically significant since abnormal RBC and spleen or bone marrow lesions were not noted.

In the blood chemistry, although potassium was decreased in males of the 1,000 mg/kg group without diarrhea and an electrolyte imbalance, this change was not considered to be related to treatment.

In the organ weights, absolute adrenal weights were increased in males of the 1,000 mg/kg group without relative weight changes and histopathological lesion. This was considered to be a secondary change related to higher body weight compared to the control value.

In the histopathological examinations, unilateral pelvic dilatation in the kidney in one male and aplasia of the left lobe and ectopic thymic tissue in the thyroid in one female were single occurrences, and the same changes were observed in the vehicle control groups. They were considered to be no treatment-related. Although hyperplasia of the lymphoid cells in the spleen was observed in one female of the 1,000 mg/kg group, this was considered to be unrelated to treatment since it was a single occurrence and limited change.

In the recovery groups, the changes of hemoglobin conc. and reticulocyte count disappeared after 14 days recovery period.

The 'No-Observed-Adverse-Effect Level' (NOAEL) was considered to be 1,000 mg/kg/day. The 'No-Observed-Effect Level' (NOEL) was considered to be 250 mg/kg/day due to decreased hemoglobin conc. and increased reticulocyte count without abnormal RBC.

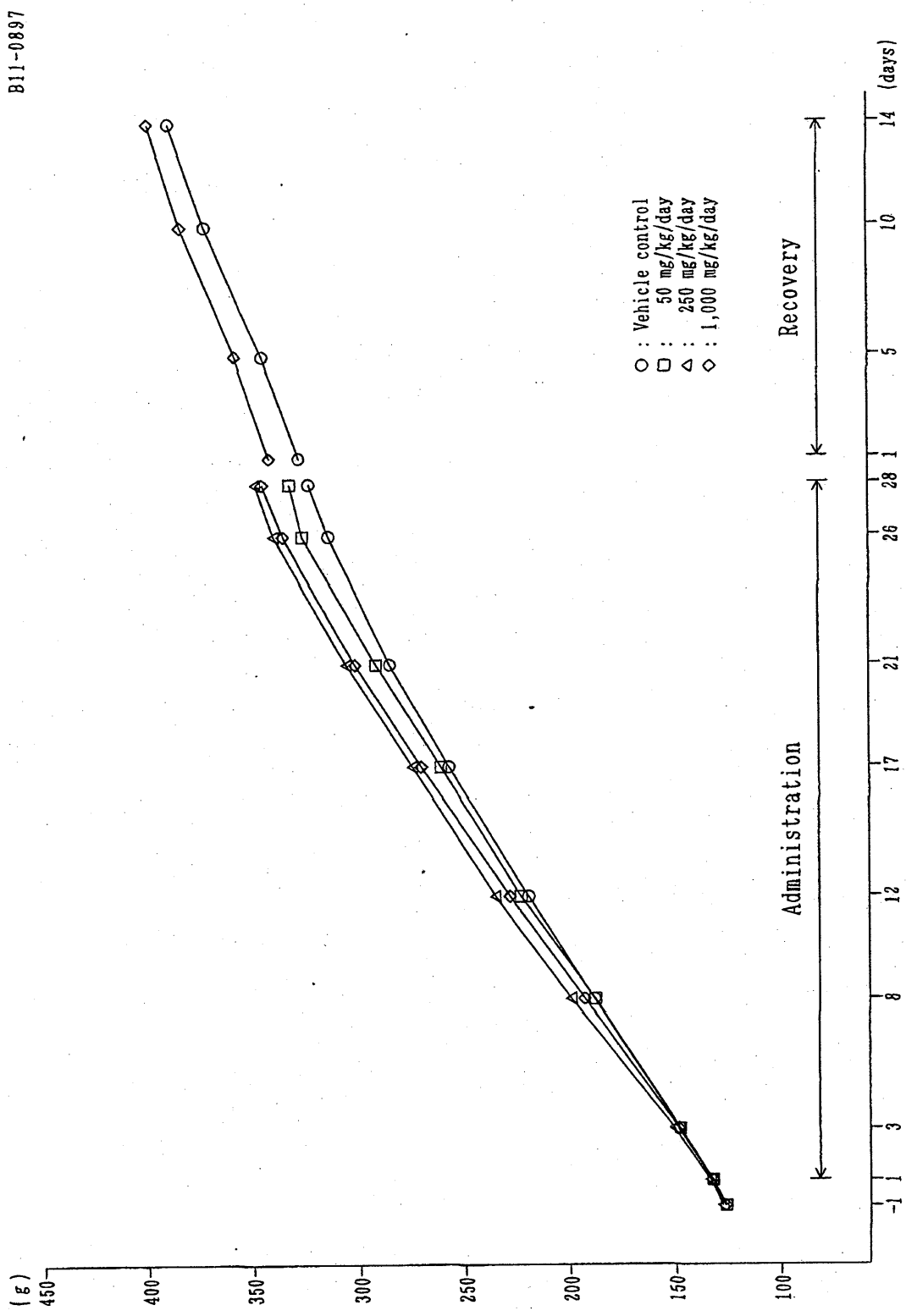


Fig. 1-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Male

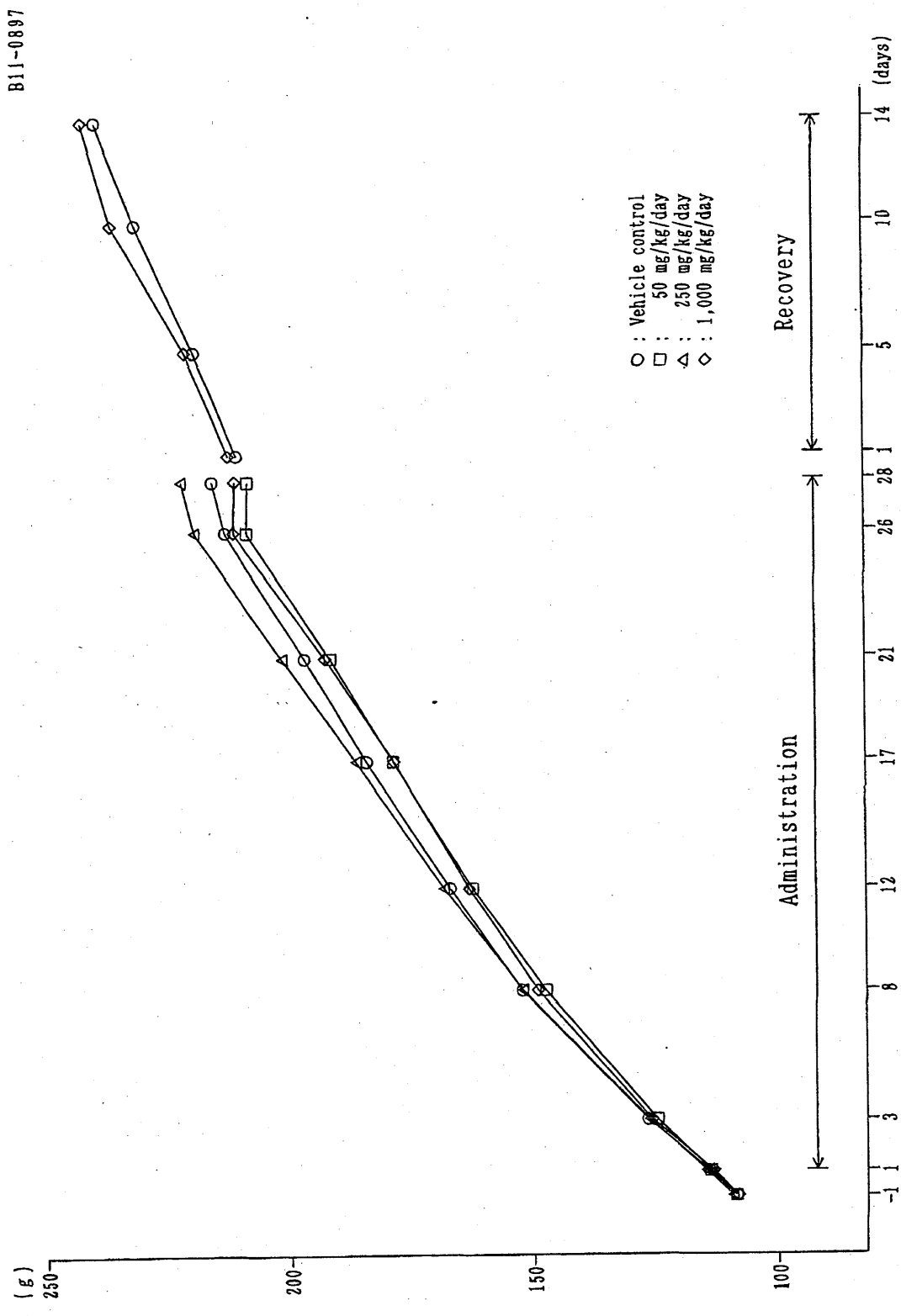


Fig. 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights : Female

B11-0897

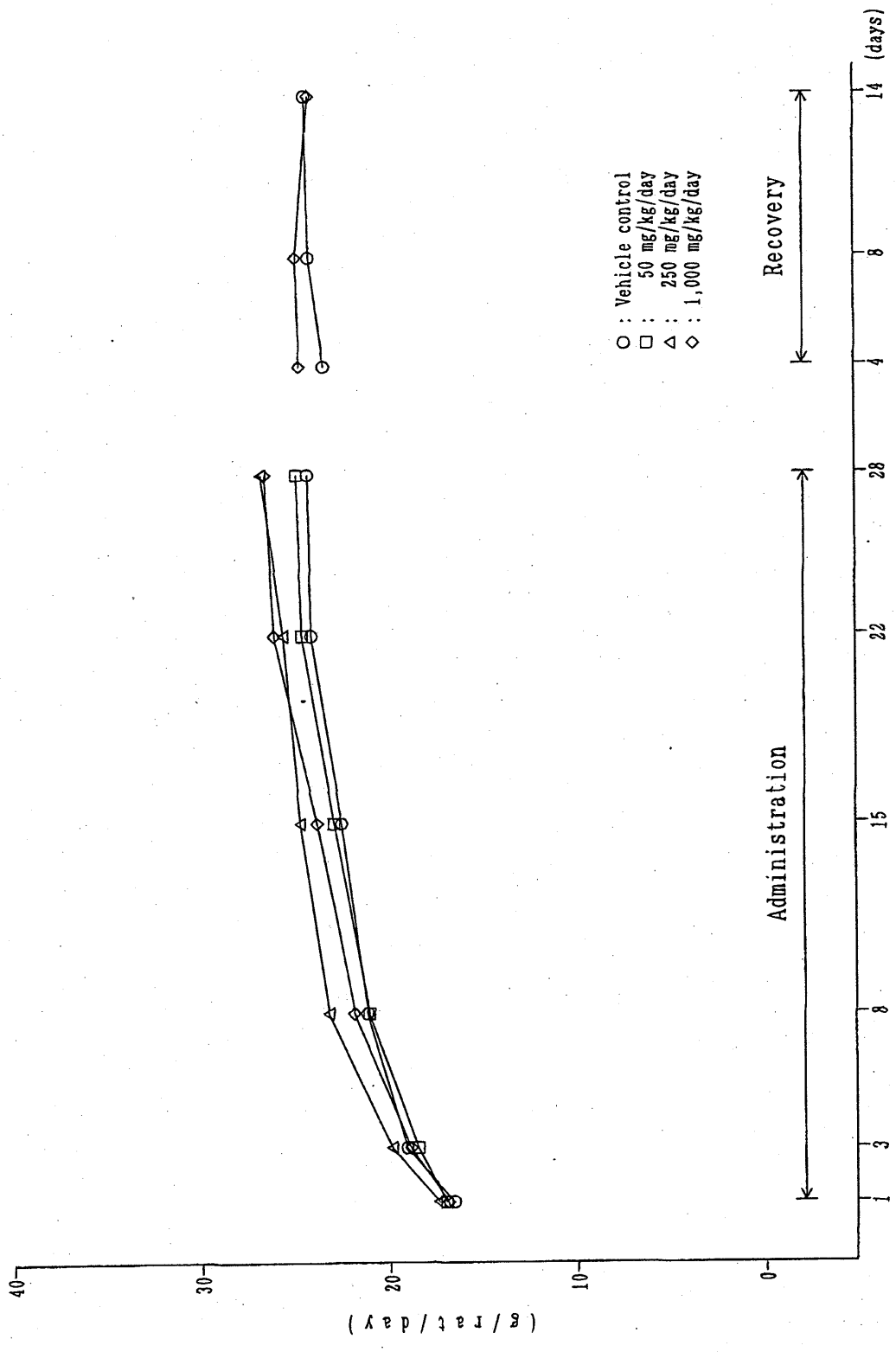


Fig. 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes : Male

B11-0897

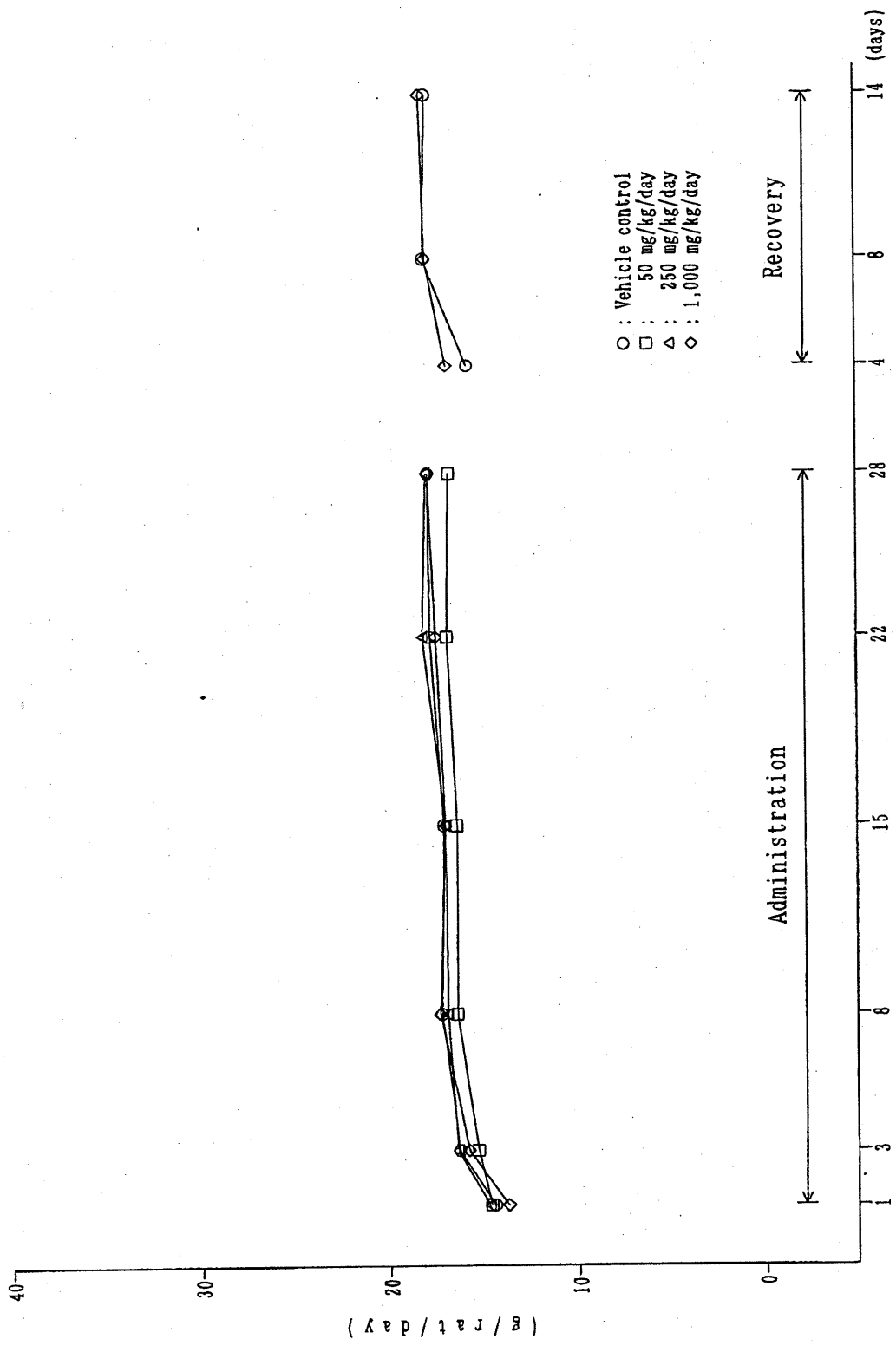


Fig. 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes : Female

Table 1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of clinical signs

Sex	Signs	Administration Period						Recovery Period	
	mg/kg/day	VC	VC (R)	50	250	1,000	1,000 (R)	VC	1,000
Male		ta	ta	ta	ta	ta	ta	ta	ta
		5[a)]	5	5	5	5	5	5	5
	No abnormalities detected	5	5	5	4	5	5	5	5
	Loss of hair				1				
Female		ta	ta	ta	ta	ta	ta	ta	ta
		5[a)]	5	5	5	5	5	5	5
	No abnormalities detected	5	5	5	5	5	5	5	5

a) Number of animals examined.
VC, Vehicle control; (R), Recovery
ta, terminal autopsy.

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

REMOVAL FROM CAGE		
Ease of removal		
	-2	No reaction
	-1	Very easy
	0	Easy (slight resistance)
	+1	Difficult
	+2	Very difficult
Vocalization		
	0	None
	+1	Vocalization during handling
	+2	Continuous vocalization
HANDLING OBSERVATIONS		
Muscle tone		
	-1	Decreased
	0	Normal
	+1	Increased
Subnormal temperature		
	-	Absent
	+	Present
Piloerection		
	-	Absent
	+	Present
Staining hair		
	-	Absent
	+	Present
Unkempt hair		
	-	Absent
	+	Present
Paleness		
	-	Absent
	+	Present
Reddening		
	-	Absent
	+	Present
Cyanosis		
	-	Absent
	+	Present
Lacrimation		
	-	Absent
	+	Present

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

HANDLING OBSERVATIONS-continued		
	Exophthalmos	
	-	Absent
	+	Present
	Pupillary size	
	-1	*Miosis*
	0	Normal
	+1	Mydriasis
	Salivation	
	-	Absent
	+	Present
	Secretion	
	-	*Absent*
	+	Present
OBSERVATIONS IN ARENA		
	Posture	
	0	Normal
	+1	Crouching position or hunchback position
	+2	*Prone position or lateral position*
	Motor activity	
	-2	Significantly decreased
	-1	Decreased
	0	Normal
	+1	Increased
	+2	Significantly increased
	Respiration	
	0	Normal
	+1	Slightly insufficiency
	+2	Moderately insufficiency
	+3	Severely insufficiency
	Lid closure	
	-	Absent
	+	Present
	Gait	
	-	Normal
	S	Staggering gait
	T	Tip toe gait
	P	Shuffling (paralytic) gait
	GD	Gait disturbance

Table 2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations (scoring scale for detailed clinical observations)

OBSERVATIONS IN ARENA-continued	
Tremor/twitch/convulsion	
0	None
+1	*Tremor*
+2	Twitch or convulsion
+3	*Systematic tonic convulsion (opisthotonus or episthotonus etc.)*
Stereotypic behavior	
-	None
C	Circling
G	Grooming
S	Sniffing
H	Head bobbing
Abnormal behavior	
-	None
S	Self-biting
B	Backing
C	Circling
R	Rolling
W	Writhing
V	Vocalization
ST	Straub tail
T	Tail lashing behavior

Table 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Removal from cage: Ease of removal -2	-1	0	+1	+2	Removal from cage: Vocalization 0	+1	+2
Male	Predosing	Vehicle control	10	0	0	10	0	0	10	0	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	0	10	0	0	10	0	0
	week 1	Vehicle control	10	0	0	10	0	0	7	3	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	0	10	0	0	10	0	0
	week 2	Vehicle control	10	0	0	10	0	0	10	0	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	0	10	0	0	10	0	0
	week 3	Vehicle control	10	0	0	10	0	0	9	1	0
		50	5	0	0	5	0	0	4	1	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	0	10	0	0	8	2	0
	week 4	Vehicle control	10	0	0	10	0	0	10	0	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	1	9	0	0	8	2	0
	Recovery week 1	Vehicle control	5	0	0	5	0	0	3	2	0
		1,000	5	0	0	5	0	0	4	1	0
	Recovery week 2	Vehicle control	5	0	0	5	0	0	3	2	0
		1,000	5	0	0	5	0	0	4	1	0

Table 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Removal from cage							
				Ease of removal					Vocalization		
				-2	-1	0	+1	+2	0	+1	+2
Female	Predosing	Vehicle control	10	0	0	10	0	0	9	1	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	0	10	0	0	8	2	0
	week 1	Vehicle control	10	0	0	10	0	0	10	0	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	0	10	0	0	9	1	0
	week 2	Vehicle control	10	0	0	10	0	0	10	0	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	5	0	0
		1,000	10	0	0	10	0	0	6	4	0
	week 3	Vehicle control	10	0	0	10	0	0	8	2	0
		50	5	0	0	5	0	0	3	2	0
		250	5	0	0	5	0	0	4	1	0
		1,000	10	0	0	10	0	0	6	4	0
	week 4	Vehicle control	10	0	0	10	0	0	10	0	0
		50	5	0	0	5	0	0	5	0	0
		250	5	0	0	5	0	0	3	2	0
		1,000	10	0	0	10	0	0	7	3	0
	Recovery week 1	Vehicle control	5	0	0	5	0	0	5	0	0
		1,000	5	0	0	5	0	0	3	2	0
	Recovery week 2	Vehicle control	5	0	0	5	0	0	5	0	0
		1,000	5	0	0	5	0	0	4	1	0

Table 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Muscle tone			Subnormal temperature		Piloerection	
				-1	0	+1	-	+	-	+
Male	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0

Table 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Muscle tone			Subnormal temperature		Piloerection	
				-1	0	+1	-	+	-	+
Female	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0

Table 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations							
				Staining hair		Unkempt hair		Paleness		Reddening	
				-	+	-	+	-	+	-	+
Male	Predosing	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0	5	0

Table 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations							
				Staining hair		Unkempt hair		Paleness		Reddening	
				-	+	-	+	-	+	-	+
Female	Predosing	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0	10	0
		50	5	5	0	5	0	5	0	5	0
		250	5	5	0	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0	5	0

Table 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations					
				Cyanosis		Lacrimation		Exophthalmos	
				-	+	-	+	-	+
Male	Predosing	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0

Table 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations					
				Cyanosis		Lacrimation		Exophthalmos	
				-	+	-	+	-	+
Female	Predosing	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 1	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 2	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 3	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	week 4	Vehicle control	10	10	0	10	0	10	0
		50	5	5	0	5	0	5	0
		250	5	5	0	5	0	5	0
		1,000	10	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	5	0	5	0	5	0
		1,000	5	5	0	5	0	5	0

Table 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Pupillary size			Salivation		Secretion	
				-1	0	+1	-	+	-	+
Male	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0

Table 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Handling observations						
				Pupillary size			Salivation		Secretion	
				-1	0	+1	-	+	-	+
Female	Predosing	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 1	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 2	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 3	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	week 4	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
	Recovery week 1	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0
	Recovery week 2	Vehicle control	5	0	5	0	5	0	5	0
		1,000	5	0	5	0	5	0	5	0

Table 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena							
				Posture			Motor activity				
				0	+1	+2	-2	-1	0	+1	+2
Male	Predosing	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	5	0	0
		250	5	5	0	0	0	0	4	1	0
		1,000	10	10	0	0	0	0	10	0	0
	week 1	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	5	0	0
		250	5	5	0	0	0	0	3	2	0
		1,000	10	10	0	0	0	1	9	0	0
	week 2	Vehicle control	10	10	0	0	0	0	9	1	0
		50	5	5	0	0	0	0	4	1	0
		250	5	5	0	0	0	1	3	1	0
		1,000	10	10	0	0	0	0	10	0	0
	week 3	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	5	0	0
		250	5	5	0	0	0	0	5	0	0
		1,000	10	10	0	0	0	0	10	0	0
	week 4	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	5	0	0
		250	5	5	0	0	0	0	5	0	0
		1,000	10	10	0	0	0	1	9	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	5	0	0
		1,000	5	5	0	0	0	0	5	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	4	1	0
		1,000	5	5	0	0	0	0	5	0	0

Table 2-12 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena							
				Posture			Motor activity				
				0	+1	+2	-2	-1	0	+1	+2
Female	Predosing	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	5	0	0
		250	5	5	0	0	0	0	4	1	0
		1,000	10	10	0	0	0	0	10	0	0
	week 1	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	5	0	0
		250	5	5	0	0	0	0	5	0	0
		1,000	10	10	0	0	0	0	10	0	0
	week 2	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	4	1	0
		250	5	5	0	0	0	0	5	0	0
		1,000	10	10	0	0	0	0	9	1	0
	week 3	Vehicle control	10	10	0	0	0	0	9	1	0
		50	5	5	0	0	0	0	4	1	0
		250	5	5	0	0	0	0	4	1	0
		1,000	10	10	0	0	0	0	9	1	0
	week 4	Vehicle control	10	10	0	0	0	0	10	0	0
		50	5	5	0	0	0	0	5	0	0
		250	5	5	0	0	0	0	3	2	0
		1,000	10	10	0	0	0	0	10	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	4	1	0
		1,000	5	5	0	0	0	0	4	1	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	5	0	0
		1,000	5	5	0	0	0	0	4	1	0

Table 2-13 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena					
				Respiration				Lid closure	
				0	+1	+2	+3	-	+
Male	Predosing	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 1	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 2	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 3	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 4	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	Recovery week 1	Vehicle control	5	5	0	0	0	5	0
		1,000	5	5	0	0	0	5	0
	Recovery week 2	Vehicle control	5	5	0	0	0	5	0
		1,000	5	5	0	0	0	5	0

Table 2-14 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena					
				Respiration				Lid closure	
				0	+1	+2	+3	-	+
Female	Predosing	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 1	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 2	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 3	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	week 4	Vehicle control	10	10	0	0	0	10	0
		50	5	5	0	0	0	5	0
		250	5	5	0	0	0	5	0
		1,000	10	10	0	0	0	10	0
	Recovery week 1	Vehicle control	5	5	0	0	0	5	0
		1,000	5	5	0	0	0	5	0
	Recovery week 2	Vehicle control	5	5	0	0	0	5	0
		1,000	5	5	0	0	0	5	0

Table 2-15 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Gait				
				-	S	T	P	GD
Male	Predosing	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0

Table 2-16 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena				
				Gait				
				-	S	T	P	GD
Female	Predosing	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0

Table 2-17 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Tremor/twitch/convulsion 0	+1	+2	+3	Defecation (count/min)[a]	Urination (count/min)[a]
Male	Predosing	Vehicle control	10	10	0	0	0	0.3 ±0.67	1.4 ±1.71
		50	5	5	0	0	0	0.0 ±0.00	3.6 ±4.16
		250	5	5	0	0	0	1.0 ±1.22	1.2 ±1.79
		1,000	10	10	0	0	0	0.1 ±0.32	1.9 ±2.64
	week 1	Vehicle control	10	10	0	0	0	0.2 ±0.42	0.9 ±1.20
		50	5	5	0	0	0	0.6 ±1.34	0.8 ±1.30
		250	5	5	0	0	0	0.4 ±0.89	2.0 ±1.41
		1,000	10	10	0	0	0	0.1 ±0.32	0.3 ±0.67
	week 2	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.3 ±0.95
		50	5	5	0	0	0	0.0 ±0.00	1.6 ±1.14
		250	5	5	0	0	0	0.4 ±0.89	1.0 ±1.41
		1,000	10	10	0	0	0	0.1 ±0.32	0.4 ±0.52
	week 3	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.5 ±0.97
		50	5	5	0	0	0	0.2 ±0.45	0.6 ±0.89
		250	5	5	0	0	0	0.4 ±0.89	0.0 ±0.00
		1,000	10	10	0	0	0	0.4 ±0.97	0.3 ±0.48
	week 4	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.7 ±1.57
		50	5	5	0	0	0	0.0 ±0.00	0.2 ±0.45
		250	5	5	0	0	0	0.4 ±0.89	0.0 ±0.00
		1,000	10	10	0	0	0	0.1 ±0.32	0.2 ±0.42
	Recovery week 1	Vehicle control	5	5	0	0	0	0.2 ±0.45	0.6 ±1.34
		1,000	5	5	0	0	0	0.0 ±0.00	0.4 ±0.55
	Recovery week 2	Vehicle control	5	5	0	0	0	0.0 ±0.00	3.4 ±3.85
		1,000	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00

a) Mean ±S.D.

* Significantly different from vehicle control at P<0.05.

** Significantly different from vehicle control at P<0.01.

Table 2-18 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Tremor/twitch/convulsion 0	+1	+2	+3	Defecation (count/min)[a]	Urination (count/min)[a]
Female	Predosing	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.5 ±0.53
		50	5	5	0	0	0	0.0 ±0.00	4.8 ±6.14
		250	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		1,000	10	10	0	0	0	0.3 ±0.95	0.4 ±0.97
	week 1	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.2 ±0.63
		50	5	5	0	0	0	0.4 ±0.89	2.0 ±2.83
		250	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		1,000	10	10	0	0	0	0.0 ±0.00	0.7 ±2.21
	week 2	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.4 ±1.26
		50	5	5	0	0	0	0.0 ±0.00	1.2 ±2.68
		250	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		1,000	10	10	0	0	0	0.0 ±0.00	0.7 ±2.21
	week 3	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.0 ±0.00
		50	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		250	5	5	0	0	0	0.0 ±0.00	0.4 ±0.89
		1,000	10	10	0	0	0	0.0 ±0.00	0.3 ±0.95
	week 4	Vehicle control	10	10	0	0	0	0.0 ±0.00	0.0 ±0.00
		50	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		250	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		1,000	10	10	0	0	0	0.0 ±0.00	0.1 ±0.32
	Recovery week 1	Vehicle control	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		1,000	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
	Recovery week 2	Vehicle control	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00
		1,000	5	5	0	0	0	0.0 ±0.00	0.0 ±0.00

a) Mean ±S.D.

* Significantly different from vehicle control at P<0.05.

** Significantly different from vehicle control at P<0.01.

Table 2-19 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Stereotypic behavior -	C	G	S	H
Male	Predosing	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0

Table 2-20 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Stereotypic behavior: -	C	G	S	H
Female	Predosing	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0
		50	5	5	0	0	0	0
		250	5	5	0	0	0	0
		1,000	10	10	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0
		1,000	5	5	0	0	0	0

Table 2-21 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Abnormal behavior: -	S	B	C	R	W	V	ST	T
Male	Predosing	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	0	0	0	0
		1,000	5	5	0	0	0	0	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	0	0	0	0
		1,000	5	5	0	0	0	0	0	0	0	0

Table 2-22 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of detailed clinical observations

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Observations in arena: Abnormal behavior: -	S	B	C	R	W	V	ST	T
Female	Predosing	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 1	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 2	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 3	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	week 4	Vehicle control	10	10	0	0	0	0	0	0	0	0
		50	5	5	0	0	0	0	0	0	0	0
		250	5	5	0	0	0	0	0	0	0	0
		1,000	10	10	0	0	0	0	0	0	0	0
	Recovery week 1	Vehicle control	5	5	0	0	0	0	0	0	0	0
		1,000	5	5	0	0	0	0	0	0	0	0
	Recovery week 2	Vehicle control	5	5	0	0	0	0	0	0	0	0
		1,000	5	5	0	0	0	0	0	0	0	0

Table 3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897
Summary of reflex (scoring scale for reflex)

SENSORIMOTOR FUNCTION	
Approach contact/touch response	
-1	No reaction
0	Normal
+1	Hyper reaction
Pinna response	
-1	No reaction
0	Normal
+1	Hyper reaction
Pain response (tail pinch)	
-1	No reaction
0	Normal
+1	Hyper reaction
Pupillary reflex	
+	Normal
-	Abnormal reaction
Air righting reflex	
+	Normal
-	Abnormal reaction

Table 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897
Summary of reflex

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Sensorimotor function					
				Approach contact/ touch response			Pinna response		
				-1	0	+1	-1	0	+1
Male	week 4	Vehicle control	10	0	10	0	0	10	0
		50	5	0	5	0	0	5	0
		250	5	0	5	0	0	5	0
		1,000	10	0	10	0	0	10	0
Female	week 4	Vehicle control	10	0	10	0	0	10	0
		50	5	0	5	0	0	5	0
		250	5	0	5	0	0	5	0
		1,000	10	0	10	0	0	10	0

Table 3-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Summary of reflex

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Sensorimotor function						
				Pain response (tail pinch)			Pupillary reflex		Air righting reflex	
				-1	0	+1	+	-	+	-
Male	week 4	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0
Female	week 4	Vehicle control	10	0	10	0	10	0	10	0
		50	5	0	5	0	5	0	5	0
		250	5	0	5	0	5	0	5	0
		1,000	10	0	10	0	10	0	10	0

Table 4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897
Summary of grip strength

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Forelimb (g)	Hindlimb (g)
Male	week 4	Vehicle control	10	426 ±33	411 ±27
		50	5	403 ±32	390 ±25
		250	5	397 ±21	401 ±39
		1,000	10	422 ±29	411 ±33
Female	week 4	Vehicle control	10	344 ±19	356 ±22
		50	5	338 ±15	377 ±11
		250	5	358 ±14	359 ±21
		1,000	10	346 ±23	366 ±26

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897
Summary of motor activity

Sex	Period	Exp. group (mg/kg/day)	Number of animals	Interval (min) 0-10	10-20	20-30	30-40	40-50	50-60	Total
Male	week 4	Vehicle control	10	205 ±28	126 ±50	73 ±51	40 ±34	43 ±58	25 ±38	512 ±157
		50	5	233 ±54	81 ±36	41 ±36	27 ±25	18 ±32	25 ±39	425 ±157
		250	5	195 ±114	146 ±30	63 ±52	51 ±54	50 ±33	38 ±38	542 ±176
		1,000	10	231 ±55	119 ±51	70 ±54	39 ±45	24 ±42	17 ±27	501 ±194
Female	week 4	Vehicle control	10	225 ±52	170 ±93	114 ±97	84 ±97	94 ±128	66 ±102	753 ±497
		50	5	179 ±55	90 ±49	110 ±52	61 ±38	52 ±62	29 ±27	521 ±181
		250	5	242 ±72	100 ±82	44 ±58	14 ±24	58 ±62	31 ±37	491 ±186
		1,000	10	223 ±31	81 * ±36	39 ±38	34 ±38	19 ±45	36 ±53	433 ±93
	Recovery week 2	Vehicle control	5	159 ±43	89 ±54	53 ±51	31 ±42	24 ±33	27 ±28	383 ±184
		1,000	5	197 ±26	99 ±61	55 ±62	84 ±41	73 ±38	21 ±26	529 ±116

Mean ±S.D.

* Significantly different from vehicle control at P<0.05.

** Significantly different from vehicle control at P<0.01.

Table 6-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of body weights(g)

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Administration period								
			−1	1	3	8	12	17	21	26	28 (days)
Male	Vehicle control	10	126.1 ± 5.9	132.3 ± 6.5	148.1 ± 7.8	188.6 ± 11.3	219.3 ± 13.1	257.8 ± 14.5	286.0 ± 14.0	314.9 ± 16.9	324.0 ± 16.0
	50	5	126.2 ± 6.0	132.3 ± 5.7	147.8 ± 8.1	188.1 ± 12.6	222.9 ± 14.0	261.7 ± 18.1	292.5 ± 20.5	327.1 ± 23.0	333.3 ± 22.8
	250	5	127.9 ± 7.3	133.7 ± 7.1	150.7 ± 7.0	199.3 ± 8.8	235.3 ± 11.1	275.2 ± 11.7	306.5 ± 12.4	340.7 ± 13.0	349.2 ± 12.8
	1,000	10	126.7 ± 7.1	132.7 ± 7.6	148.7 ± 10.7	193.0 ± 17.0	228.2 ± 19.9	271.0 ± 22.5	302.4 ± 23.8	336.3 ± 26.6	346.0 ± 27.1
Female	Vehicle control	10	108.7 ± 3.5	114.3 ± 4.6	126.6 ± 5.7	152.3 ± 9.8	167.2 ± 12.5	184.4 ± 15.8	196.9 ± 20.6	213.1 ± 22.1	215.7 ± 21.9
	50	5	108.7 ± 2.8	113.9 ± 2.9	124.7 ± 2.8	147.5 ± 4.6	162.5 ± 6.1	179.0 ± 7.4	191.7 ± 8.2	208.6 ± 8.1	208.4 ± 10.5
	250	5	109.4 ± 3.0	114.8 ± 1.8	126.3 ± 3.3	152.1 ± 4.4	168.5 ± 5.4	186.5 ± 10.4	201.5 ± 13.1	219.3 ± 11.0	222.0 ± 14.8
	1,000	10	108.3 ± 3.1	113.3 ± 4.1	125.8 ± 5.6	149.1 ± 6.1	163.2 ± 8.4	178.8 ± 11.9	192.7 ± 13.4	211.3 ± 12.3	211.0 ± 14.9

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 6-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of body weights(g)

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Recovery period 1	5	10	14 (days)
Male	Vehicle control	5	328.6 ± 18.5	346.2 ± 18.4	373.5 ± 20.0	390.7 ± 23.5
	1,000	5	342.6 ± 23.6	359.1 ± 25.5	384.9 ± 29.0	400.8 ± 33.9
Female	Vehicle control	5	210.6 ± 22.7	219.4 ± 25.2	231.5 ± 25.5	239.7 ± 26.6
	1,000	5	212.3 ± 15.0	221.2 ± 13.6	236.4 ± 10.4	242.5 ± 11.8

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 7-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of food intakes(g/rat/day)

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Administration period 1	3	8	15	22	28 (days)
Male	Vehicle control	10	16.6 ± 1.6	19.1 ± 1.3	21.2 ± 1.6	22.6 ± 1.3	24.2 ± 1.2	24.4 ± 1.2
	50	5	17.0 ± 1.8	18.5 ± 1.3	21.1 ± 1.6	23.0 ± 1.2	24.7 ± 1.6	25.0 ± 1.7
	250	5	17.4 ± 1.0	19.9 ± 0.6	23.3 ± 0.8	24.8 ± 0.3	25.7 ± 1.0	26.9* ± 0.8
	1,000	10	16.9 ± 1.7	18.9 ± 2.0	21.9 ± 2.3	23.9 ± 2.4	26.2 ± 2.7	26.7 ± 3.2
Female	Vehicle control	10	14.4 ± 1.1	16.3 ± 1.5	17.2 ± 1.4	17.1 ± 1.4	17.8 ± 2.1	17.9 ± 1.8
	50	5	14.6 ± 1.2	15.3 ± 0.5	16.4 ± 1.0	16.4 ± 0.7	16.9 ± 1.0	16.8 ± 0.9
	250	5	14.7 ± 0.7	16.4 ± 1.1	16.9 ± 1.0	17.0 ± 1.0	18.2 ± 1.2	18.0 ± 1.5
	1,000	10	13.7 ± 1.2	15.8 ± 1.4	17.3 ± 0.8	17.0 ± 1.0	17.5 ± 1.1	17.9 ± 1.3

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 7-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897
Summary of food intakes(g/rat/day)

Sex	Exp.group (mg/kg/day)	Number of animals	Recovery period 4	8	14 (days)
Male	Vehicle control	5	23.5 ± 1.4	24.3 ± 1.7	24.5 ± 1.6
	1,000	5	24.8 ± 3.4	25.0 ± 3.0	24.3 ± 2.6
Female	Vehicle control	5	15.8 ± 2.9	18.1 ± 2.0	18.0 ± 1.5
	1,000	5	16.9 ± 1.5	18.0 ± 1.4	18.3 ± 0.6

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of hematological examinations

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Male	Vehicle control	5	757 ± 27	104 ± 18	15.4 ± 0.3	44.8 ± 1.2	59.2 ± 1.2	20.4 ± 0.4	34.4 ± 0.2	102.5 ± 2.7	2.6 ±0.4	18.0 ± 4.0	29.3 ± 2.7
	50	5	765 ± 34	104 ± 4	15.3 ± 0.5	45.1 ± 1.6	59.0 ± 1.8	20.1 ± 0.7	34.0 ± 0.4	106.1 ± 8.9	2.6 ±0.4	18.9 ± 3.1	32.4 ± 4.3
	250	5	781 ± 37	111 ± 37	15.6 ± 0.5	46.1 ± 1.3	59.1 ± 2.5	20.0 ± 0.9	33.9* ± 0.2	111.6 ± 8.7	2.7 ±0.3	20.5 ± 2.0	33.8 ± 2.4
	1,000	5	745 ± 22	113 ± 17	15.2 ± 0.4	44.7 ± 1.4	59.9 ± 1.7	20.4 ± 0.6	34.1 ± 0.2	102.9 ± 8.4	3.0 ±0.3	17.8 ± 2.7	30.1 ± 2.7
	Recovery Vehicle control	5	817 ± 23	124 ± 24	15.7 ± 0.4	46.0 ± 0.8	56.3 ± 1.9	19.3 ± 0.6	34.2 ± 0.4	96.3 ± 3.9	2.3 ±0.5	18.8 ± 1.8	33.7 ± 3.7
	1,000	5	825 ± 35	122 ± 21	15.8 ± 0.7	46.2 ± 1.7	56.0 ± 1.5	19.2 ± 0.5	34.2 ± 0.4	99.8 ± 5.4	1.8 ±0.3	20.9 ± 4.8	35.4 ± 6.7
Female	Vehicle control	5	766 ± 20	97 ± 16	15.4 ± 0.3	44.4 ± 0.5	57.9 ± 1.4	20.1 ± 0.5	34.7 ± 0.2	111.2 ± 8.4	1.8 ±0.2	14.1 ± 0.4	20.4 ± 0.9
	50	5	770 ± 36	94 ± 34	15.3 ± 0.3	44.2 ± 1.2	57.4 ± 1.3	19.9 ± 0.7	34.7 ± 0.6	106.7 ± 7.7	1.7 ±0.3	13.8 ± 0.5	22.7 ± 2.0
	250	5	776 ± 17	98 ± 30	15.5 ± 0.3	45.1 ± 1.0	58.1 ± 1.6	19.9 ± 0.5	34.4 ± 0.3	104.6 ± 7.6	2.1 ±0.4	14.0 ± 0.7	22.3 ± 2.4
	1,000	5	746 ± 19	105 ± 13	14.9* ± 0.3	43.1 ± 1.5	57.7 ± 1.5	19.9 ± 0.4	34.5 ± 0.5	112.7 ± 7.0	2.4* ±0.3	13.4 ± 0.6	21.7 ± 2.5
	Recovery Vehicle control	5	814 ± 25	71 ± 19	15.6 ± 0.5	44.0 ± 1.3	54.0 ± 1.1	19.1 ± 0.5	35.4 ± 0.3	124.7 ± 5.6	1.8 ±0.3	13.5 ± 0.5	23.9 ± 1.3
	1,000	5	798 ± 23	91 ± 25	15.5 ± 0.1	43.7 ± 0.5	54.8 ± 1.8	19.4 ± 0.6	35.4 ± 0.4	127.3 ± 11.4	2.2 ±0.3	14.1 ± 0.4	23.2 ± 2.1

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of hematological examinations

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Differentiation of leukocyte (%)					
			Neutro	Eosino	Baso	Lymph	Mono	LUC
Male	Vehicle control	5	18.5 ± 3.7	0.9 ±0.2	0.3 ±0.0	76.8 ± 4.2	2.7 ±0.9	0.8 ±0.2
	50	5	19.3 ± 3.3	0.9 ±0.3	0.3 ±0.1	76.1 ± 2.7	2.7 ±0.6	0.8 ±0.6
	250	5	12.9 ± 6.6	0.8 ±0.2	0.2 ±0.1	82.7 ± 7.2	2.6 ±0.8	0.8 ±0.3
	1,000	5	17.6 ± 3.0	1.1 ±0.1	0.2 ±0.1	78.0 ± 3.3	2.3 ±0.8	0.8 ±0.3
	Recovery Vehicle control	5	16.3 ± 4.9	0.7 ±0.2	0.2 ±0.2	79.1 ± 5.7	2.7 ±1.0	0.9 ±0.5
	1,000	5	10.9 ± 3.7	0.7 ±0.2	0.2 ±0.1	84.9 ± 4.5	2.5 ±0.7	0.8 ±0.1
Female	Vehicle control	5	14.7 ± 4.9	1.5 ±0.4	0.2 ±0.1	80.2 ± 4.6	2.6 ±0.5	0.9 ±0.2
	50	5	14.8 ± 4.4	1.0 ±0.3	0.2 ±0.0	80.0 ± 4.5	3.0 ±0.5	1.0 ±0.2
	250	5	17.4 ± 5.8	1.4 ±0.4	0.2 ±0.1	77.6 ± 5.7	2.4 ±0.3	1.0 ±0.3
	1,000	5	21.0 ± 4.2	1.0 ±0.4	0.2 ±0.1	74.1 ± 3.7	2.8 ±0.6	1.0 ±0.3
	Recovery Vehicle control	5	15.7 ± 3.5	1.4 ±0.5	0.1 ±0.1	80.2 ± 4.4	1.9 ±0.9	0.7 ±0.1
	1,000	5	16.3 ± 7.0	1.2 ±0.4	0.2 ±0.1	79.6 ± 7.3	1.8 ±0.4	0.9 ±0.2

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Male	Vehicle control	5	74 ± 5	26 ± 3	493 ± 51	37 ± 2	0.7 ±0.2	57 ± 6	60 ±18	125 ± 9	5.6 ±0.1	2.9 ±0.1	1.05 ±0.08
	50	5	79 ± 8	23 ± 3	425 ± 82	40 ± 7	0.8 ±0.3	54 ± 9	56 ±12	127 ± 15	5.7 ±0.1	2.9 ±0.1	1.03 ±0.10
	250	5	84 ±11	28 ± 5	512 ± 80	44 ± 17	0.6 ±0.2	52 ± 4	50 ±19	135 ± 20	5.7 ±0.2	2.9 ±0.1	1.01 ±0.03
	1,000	5	70 ±10	24 ± 3	456 ± 56	45 ± 9	0.6 ±0.2	48 ± 8	63 ±22	145 ± 7	5.5 ±0.2	2.9 ±0.0	1.12 ±0.10
	Recovery												
	Vehicle control	5	76 ± 5	26 ± 3	295 ± 28	44 ± 12	0.8 ±0.1	49 ± 4	46 ±18	146 ± 6	5.6 ±0.2	2.7 ±0.1	0.94 ±0.07
	1,000	5	74 ±10	23 ± 5	321 ± 72	50 ± 10	0.7 ±0.2	48 ±13	56 ±17	145 ± 10	5.6 ±0.2	2.8 ±0.1	1.01 ±0.08
Female	Vehicle control	5	73 ± 9	23 ± 2	285 ± 54	339 ± 37	0.9 ±0.2	70 ± 3	19 ± 8	117 ± 5	5.8 ±0.2	3.1 ±0.1	1.13 ±0.07
	50	5	75 ± 9	19 ± 2	271 ± 66	334 ±134	0.9 ±0.8	69 ±20	25 ±12	114 ± 8	5.8 ±0.2	3.1 ±0.1	1.12 ±0.05
	250	5	68 ± 3	19 ± 2	246 ± 58	314 ± 71	1.0 ±0.2	64 ± 5	28 ±18	133 ± 27	5.9 ±0.2	3.2 ±0.1	1.16 ±0.07
	1,000	5	68 ± 7	23 ± 8	253 ± 33	299 ±108	1.0 ±0.2	69 ± 6	23 ± 6	124 ± 11	5.9 ±0.3	3.1 ±0.1	1.14 ±0.12
	Recovery												
	Vehicle control	5	69 ± 6	19 ± 5	214 ± 59	375 ±126	1.0 ±0.2	66 ±14	22 ±11	143 ± 30	6.0 ±0.4	3.0 ±0.2	1.03 ±0.12
	1,000	5	74 ± 7	22 ± 4	215 ± 36	393 ±199	1.1 ±0.1	57 ± 8	15 ± 7	133 ± 12	6.0 ±0.3	3.0 ±0.1	1.03 ±0.08

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of blood chemical examinations

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Male	Vehicle control	5	14.6 ± 1.5	0.22 ±0.02	0.07 ±0.02	9.7 ± 0.2	8.0 ±0.7	143 ± 1	4.1 ±0.3	106.1 ± 2.0
	50	5	14.2 ± 1.5	0.21 ±0.02	0.06 ±0.02	9.8 ± 0.2	7.9 ±0.4	143 ± 1	4.6 ±0.4	106.2 ± 1.2
	250	5	15.3 ± 3.9	0.21 ±0.03	0.07 ±0.02	10.0 ± 0.2	8.3 ±0.3	142 ± 0	4.4 ±0.1	105.8 ± 1.0
	1,000	5	15.1 ± 3.0	0.24 ±0.05	0.07 ±0.01	10.0 ± 0.3	8.1 ±0.4	141** ± 1	4.2 ±0.1	104.6 ± 2.4
	Recovery									
	Vehicle control	5	16.3 ± 2.3	0.25 ±0.02	0.06 ±0.01	9.4 ± 0.3	7.1 ±0.5	141 ± 1	4.3 ±0.3	104.5 ± 0.7
	1,000	5	16.5 ± 2.2	0.26 ±0.03	0.07 ±0.01	9.4 ± 0.2	7.2 ±0.3	142 ± 1	4.3 ±0.3	104.6 ± 0.8
Female	Vehicle control	5	16.1 ± 2.2	0.24 ±0.04	0.06 ±0.01	9.7 ± 0.3	7.3 ±0.6	141 ± 1	4.1 ±0.3	106.7 ± 1.3
	50	5	16.7 ± 1.2	0.27 ±0.02	0.06 ±0.02	9.7 ± 0.2	6.9 ±0.5	141 ± 1	3.9 ±0.3	107.6 ± 0.9
	250	5	16.3 ± 2.7	0.25 ±0.03	0.07 ±0.02	9.9 ± 0.3	7.0 ±0.6	140 ± 1	4.1 ±0.5	107.0 ± 1.1
	1,000	5	16.8 ± 2.8	0.27 ±0.03	0.06 ±0.01	9.8 ± 0.2	7.0 ±0.7	139 ± 2	4.2 ±0.3	106.2 ± 0.6
	Recovery									
	Vehicle control	5	17.2 ± 1.8	0.30 ±0.03	0.07 ±0.01	9.3 ± 0.3	5.9 ±0.4	140 ± 2	3.8 ±0.2	106.2 ± 2.6
	1,000	5	17.7 ± 0.4	0.28 ±0.04	0.07 ±0.01	9.3 ± 0.2	6.1 ±0.3	141 ± 1	4.0 ±0.3	107.0 ± 0.9

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897
Summary of urinalyses

Sex	Exp.group (mg/kg/day)	Number of animals	Urine volume (mL)	Uosm (mOsm/L)
Male	Vehicle control	5	17 ± 7	548 ± 412
	50	5	17 ± 7	514 ± 235
	250	5	16 ± 5	581 ± 392
	1,000	5	20 ± 7	449 ± 181
	Recovery			
	Vehicle control	5	9 ± 4	1405 ± 810
	1,000	5	9 ± 3	1364 ± 483
Female	Vehicle control	5	11 ± 5	818 ± 480
	50	5	9 ± 4	825 ± 386
	250	5	9 ± 3	711 ± 155
	1,000	5	8 ± 7	1315 ± 817
	Recovery			
	Vehicle control	5	6 ± 3	1174 ± 245
	1,000	5	9 ± 2	895 ± 153

Mean ±S.D.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 10-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of urinalyses

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Color SY	Color Y	Turbidity NT	pH 6.0	pH 6.5	pH 7.0	Protein −	Protein ±	Protein 1+	Protein 2+	Glucose −	Occult blood −
Male	Vehicle control	5	4	1	5	0	3	2	0	2	2	1	5	5
	50	5	4	1	5	0	4	1	0	2	3	0	5	5
	250	5	4	1	5	0	2	3	0	1	3	1	5	5
	1,000	5	5	0	5	0	4	1	0	3	2	0	5	5
	Recovery													
	Vehicle control	5	4	1	5	0	2	3	0	3	2	0	5	5
	1,000	5	2	3	5	1	3	1	0	1	4	0	5	5
Female	Vehicle control	5	3	2	5	2	3	0	1	1	2	1	5	5
	50	5	3	2	5	2	2	1	0	1	4	0	5	5
	250	5	4	1	5	1	3	1	0	2	3	0	5	5
	1,000	5	2	3	5	2	3	0	0	2	1	2	5	5
	Recovery													
	Vehicle control	5	2	3	5	3	2	0	0	4	1	0	5	5
	1,000	5	5	0	5	1	4	0	0	5	0	0	5	5

SY, Slightly yellow.
Y, Yellow.
NT, No turbidity.

Table 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of urinalyses (Urinary sediment)

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Red blood cells[a]	White blood cells[a]		Epithelial cells[a]		Casts[b]	Crystals[c]			
			0	0	1-5	0	1-5	0	−	±	+	++
Male	Vehicle control	5	5	5	0	2	3	5	4	0	1	0
	50	0	-	-	-	-	-	-	-	-	-	-
	250	0	-	-	-	-	-	-	-	-	-	-
	1,000	5	5	4	1	2	3	5	4	1	0	0
	Recovery											
	Vehicle control	0	-	-	-	-	-	-	-	-	-	-
	1,000	0	-	-	-	-	-	-	-	-	-	-
Female	Vehicle control	5	5	5	0	3	2	5	4	1	0	0
	50	0	-	-	-	-	-	-	-	-	-	-
	250	0	-	-	-	-	-	-	-	-	-	-
	1,000	5	5	4	1	3	2	5	4	1	0	0
	Recovery											
	Vehicle control	0	-	-	-	-	-	-	-	-	-	-
	1,000	0	-	-	-	-	-	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.

Table 11 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of absolute organ weights

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight a) (g)
Male	Vehicle control	5	8.88 ± 0.28	1.08 ± 0.05	2.13 ± 0.14	2.95 ± 0.18	0.69 ± 0.04	- -	1.98 ± 0.07	0.63 ± 0.11	540.1 ± 37.1	44.2 ± 2.8	300.3 ± 12.6
	50	5	9.44 ± 0.97	1.12 ± 0.07	2.41 ± 0.28	3.06 ± 0.19	0.73 ± 0.08	- -	1.95 ± 0.10	0.69 ± 0.03	495.0 ± 74.8	45.7 ± 4.0	309.6 ± 22.2
	250	5	9.65 ± 0.87	1.19 ± 0.09	2.33 ± 0.19	3.00 ± 0.14	0.69 ± 0.07	- -	1.96 ± 0.07	0.64 ± 0.07	684.5 ± 68.5	49.4 ± 5.4	323.0 ± 11.6
	1,000	5	10.17 ± 1.45	1.20 ± 0.12	2.35 ± 0.37	3.04 ± 0.18	0.73 ± 0.07	- -	2.05 ± 0.15	0.67 ± 0.08	638.0 ± 145.1	58.6** ± 11.1	326.4 ± 30.6
	Recovery												
	Vehicle control	5	9.93 ± 1.24	1.15 ± 0.11	2.52 ± 0.26	3.11 ± 0.10	0.98 ± 0.05	- -	2.00 ± 0.10	0.66 ± 0.15	517.4 ± 150.6	51.1 ± 7.7	367.8 ± 24.5
	1,000	5	10.09 ± 1.42	1.21 ± 0.09	2.43 ± 0.30	3.09 ± 0.28	0.90 ± 0.09	- -	2.04 ± 0.11	0.64 ± 0.11	468.5 ± 88.4	54.2 ± 8.7	375.3 ± 32.4
Female	Vehicle control	5	6.31 ± 0.33	0.80 ± 0.03	1.66 ± 0.15	- -	- -	87.2 ± 11.1	1.89 ± 0.04	0.49 ± 0.09	481.0 ± 72.0	70.1 ± 7.7	209.7 ± 12.7
	50	5	5.89 ± 0.41	0.75 ± 0.03	1.54 ± 0.06	- -	- -	78.0 ± 4.2	1.84 ± 0.07	0.43 ± 0.05	444.5 ± 116.5	74.1 ± 12.9	195.7 ± 6.4
	250	5	6.21 ± 0.39	0.84 ± 0.08	1.57 ± 0.15	- -	- -	81.3 ± 3.9	1.86 ± 0.06	0.43 ± 0.05	507.1 ± 114.1	66.2 ± 8.2	207.3 ± 13.5
	1,000	5	6.17 ± 0.37	0.82 ± 0.07	1.61 ± 0.07	- -	- -	83.8 ± 10.0	1.86 ± 0.07	0.47 ± 0.07	516.3 ± 53.7	67.1 ± 5.0	205.3 ± 11.5
	Recovery												
	Vehicle control	5	6.00 ± 0.75	0.76 ± 0.08	1.59 ± 0.09	- -	- -	81.7 ± 5.5	1.93 ± 0.08	0.40 ± 0.05	391.2 ± 78.3	66.1 ± 7.0	221.4 ± 25.1
	1,000	5	6.08 ± 0.52	0.75 ± 0.04	1.60 ± 0.14	- -	- -	78.4 ± 16.4	1.93 ± 0.12	0.43 ± 0.06	404.8 ± 52.1	63.9 ± 7.3	225.1 ± 9.5

Mean ±S.D.
a) Statistical analysis was not applied.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 12 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of relative organ weights

B11-0897

Sex	Exp.group (mg/kg/day)	Number of animals	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight a) (g)
Male	Vehicle control	5	2.96 ±0.09	0.36 ±0.02	0.71 ±0.03	0.99 ±0.09	0.23 ±0.02	- -	0.66 ±0.02	0.21 ±0.04	180.2 ± 15.9	14.7 ± 1.2	300.3 ± 12.6
	50	5	3.04 ±0.10	0.36 ±0.02	0.78 ±0.05	0.99 ±0.07	0.23 ±0.02	- -	0.63 ±0.04	0.22 ±0.02	159.5 ± 18.0	14.8 ± 1.7	309.6 ± 22.2
	250	5	2.99 ±0.20	0.37 ±0.03	0.72 ±0.04	0.93 ±0.04	0.21 ±0.02	- -	0.61 ±0.03	0.20 ±0.02	212.4 ± 25.5	15.3 ± 1.6	323.0 ± 11.6
	1,000	5	3.11 ±0.15	0.37 ±0.03	0.72 ±0.07	0.94 ±0.11	0.23 ±0.02	- -	0.63 ±0.05	0.21 ±0.01	194.2 ± 31.6	18.0 ± 3.9	326.4 ± 30.6
	Recovery												
	Vehicle control	5	2.69 ±0.16	0.31 ±0.02	0.68 ±0.03	0.85 ±0.05	0.26 ±0.02	- -	0.55 ±0.02	0.18 ±0.03	140.5 ± 38.8	13.9 ± 1.7	367.8 ± 24.5
	1,000	5	2.68 ±0.18	0.32 ±0.01	0.65 ±0.08	0.83 ±0.10	0.24 ±0.02	- -	0.55 ±0.04	0.17 ±0.03	124.4 ± 17.7	14.4 ± 1.8	375.3 ± 32.4
Female	Vehicle control	5	3.01 ±0.10	0.38 ±0.03	0.79 ±0.05	- -	- -	41.5 ± 3.6	0.90 ±0.04	0.23 ±0.04	229.0 ± 27.3	33.4 ± 3.0	209.7 ± 12.7
	50	5	3.01 ±0.13	0.39 ±0.02	0.78 ±0.05	- -	- -	39.9 ± 1.9	0.94 ±0.06	0.22 ±0.02	226.5 ± 56.3	37.9 ± 6.7	195.7 ± 6.4
	250	5	3.00 ±0.15	0.41 ±0.02	0.75 ±0.03	- -	- -	39.3 ± 3.3	0.90 ±0.05	0.21 ±0.02	243.9 ± 47.0	32.0 ± 3.2	207.3 ± 13.5
	1,000	5	3.00 ±0.11	0.40 ±0.04	0.78 ±0.02	- -	- -	40.8 ± 4.5	0.91 ±0.05	0.23 ±0.04	252.1 ± 30.4	32.6 ± 1.5	205.3 ± 11.5
	Recovery												
	Vehicle control	5	2.71 ±0.19	0.34 ±0.04	0.72 ±0.07	- -	- -	37.2 ± 4.2	0.88 ±0.11	0.18 ±0.02	175.9 ± 22.5	30.1 ± 4.1	221.4 ± 25.1
	1,000	5	2.70 ±0.17	0.34 ±0.01	0.71 ±0.04	- -	- -	34.7 ± 6.6	0.86 ±0.04	0.19 ±0.03	179.7 ± 20.4	28.3 ± 3.0	225.1 ± 9.5

Mean ±S.D.
a) Statistical analysis was not applied.
* Significantly different from vehicle control at P<0.05.
** Significantly different from vehicle control at P<0.01.

Table 13 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of macroscopic examinations

Findings	Male						Female						(mg/kg/day)
	Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	
	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
	5[a)]	5	5	5	5	5	5	5	5	5	5	5	
No abnormalities detected	5	3	5	4	4	5	5	5	5	5	3	5	
Glandular stomach													
Elevated region of mucosa	0	1	0	0	0	0	0	0	0	0	0	0	
Kidney													
Pelvic dilatation	0	0	0	0	1	0	0	0	0	0	0	0	
Spleen													
Nodule	0	0	0	0	0	0	0	0	0	0	1	0	
Whitish region on capsule	0	1	0	0	0	0	0	0	0	0	0	0	
Thyroid													
Decreased in size of left lobe	0	0	0	0	0	0	0	0	0	0	1	0	
Skin													
Loss of hair	0	0	0	1	0	0	0	0	0	0	0	0	

ta, terminal autopsy.

a) Number of animals examined.

Table 14-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a]	5	5	5	5	5	5	5	5	5	5	5	
Trachea														
No abnormalities detected		5/5[b]	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Lung														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Forestomach														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Glandular stomach														
No abnormalities detected		5/5	0/1	—	—	5/5	—	5/5	—	—	—	5/5	—	
Squamous epithelial cyst	+	0/5	1/1	—	—	0/5	—	0/5	—	—	—	0/5	—	
Duodenum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Jejunum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Ileum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Cecum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Colon														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Rectum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight.

Table 14-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a]	5	5	5	5	5	5	5	5	5	5	5	
Liver														
No abnormalities detected		5/5[b]	—	—	—	5/5	—	4/5	—	—	—	4/5	—	
Microgranuloma	+	0/5	—	—	—	0/5	—	1/5	—	—	—	1/5	—	
Heart														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Kidney														
No abnormalities detected		5/5	—	—	—	4/5	—	3/5	—	—	—	5/5	—	
Mineralization in cortico-medullary junction	+	0/5	—	—	—	0/5	—	1/5	—	—	—	0/5	—	
Pelvic dilatation, unilateral	+	0/5	—	—	—	1/5	—	0/5	—	—	—	0/5	—	
Subcapsular cyst formation	+	0/5	—	—	—	0/5	—	1/5	—	—	—	0/5	—	
Urinary bladder														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Testis														
No abnormalities detected		5/5	—	—	—	5/5	—							
Epididymis														
No abnormalities detected		5/5	—	—	—	5/5	—							
Prostate														
No abnormalities detected		5/5	—	—	—	5/5	—							
Seminal vesicle														
No abnormalities detected		5/5	—	—	—	5/5	—							

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight.

Table 14-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a]	5	5	5	5	5	5	5	5	5	5	5	
Ovary														
No abnormalities detected								5/5[b]	—	—	—	5/5	—	
Uterus														
No abnormalities detected								5/5	—	—	—	5/5	—	
Vagina														
No abnormalities detected								5/5	—	—	—	5/5	—	
Cerebrum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Cerebellum														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Pons														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Spinal cord														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Sciatic nerve														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Bone marrow														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Axillar lymph node														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Mesenteric lymph node														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.

Table 14-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Summary of histopathological examinations

Findings	Grade	Male						Female						(mg/kg/day)
		Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	Vehicle control	Vehicle control (Recovery)	50	250	1,000	1,000 (Recovery)	
		ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	ta	
		5[a]	5	5	5	5	5	5	5	5	5	5	5	
Spleen														
No abnormalities detected		5/5[b]	0/1	—	—	5/5	—	5/5	5/5	5/5	5/5	4/5	5/5	
Capsulitis	+	0/5	1/1	—	—	0/5	—	0/5	0/5	0/5	0/5	0/5	0/5	
Hyperplasia of lymphoid cells	++	0/5	0/1	—	—	0/5	—	0/5	0/5	0/5	0/5	1/5	0/5	
Thymus														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Pituitary gland														
No abnormalities detected		5/5	—	—	—	5/5	—	4/5	—	—	—	5/5	—	
Rathke's pouch remnant	+	0/5	—	—	—	0/5	—	1/5	—	—	—	0/5	—	
Thyroid														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	3/5	—	
Aplasia of left lobe		0/5	—	—	—	0/5	—	0/5	—	—	—	1/5	—	
Ectopic thymic tissue	+	0/5	—	—	—	0/5	—	0/5	—	—	—	1/5	—	
Parathyroid														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Adrenal														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Eye ball														
No abnormalities detected		5/5	—	—	—	5/5	—	5/5	—	—	—	5/5	—	
Skin														
No abnormalities detected		—	—	—	1/1	—	—	—	—	—	—	—	—	

ta, terminal autopsy.
a) Number of animals autopsied.
b) Number of animals affected / Number of animals examined.
—, Not examined.
+, slight; ++, moderate.

Addendum 1-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
Vehicle control

Signs	Sex	Administration Period				Recovery Period		(week)
		1	2	3	4	1	2	
No abnormalities detected	Male	1,[a] 2, 3, 4, 5, 6, 7, 8, 9, 10	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	6, 7, 8, 9, 10	6, 7, 8, 9, 10	
	Female	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	31, 32, 33, 34, 35, 36, 37, 38, 39, 40	36, 37, 38, 39, 40	36, 37, 38, 39, 40	

a) Animal number.

Addendum 1-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
50 mg/kg/day

Signs	Sex	Administration Period				Recovery Period		
		1	2	3	4	1	2	(week)
No abnormalities detected	Male	11,[a] 12, 13, 14, 15	11, 12, 13, 14, 15	11, 12, 13, 14, 15	11, 12, 13, 14, 15			
	Female	41, 42, 43, 44, 45	41, 42, 43, 44, 45	41, 42, 43, 44, 45	41, 42, 43, 44, 45			

a) Animal number.

Addendum 1-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
250 mg/kg/day

Signs	Sex	Administration Period				Recovery Period		
		1	2	3	4	1	2	(week)
No abnormalities detected	Male	16,[a] 17, 18, 19, 20	16, 17, 18, 19, 20	16, 17, 18, 19, 20	16, 17, 18, 20			
	Female	46, 47, 48, 49, 50	46, 47, 48, 49, 50	46, 47, 48, 49, 50	46, 47, 48, 49, 50			
Loss of hair(forelimb)	Male				19			
	Female							

a) Animal number.

Addendum 1-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Clinical signs of individual animals
1,000 mg/kg/day

Signs	Sex	Administration Period				Recovery Period		(week)
		1	2	3	4	1	2	
No abnormalities detected	Male	21,[a] 22, 23, 24, 25, 26, 27, 28, 29, 30	21, 22, 23, 24, 25, 26, 27, 28, 29, 30	21, 22, 23, 24, 25, 26, 27, 28, 29, 30	21, 22, 23, 24, 25, 26, 27, 28, 29, 30	26, 27, 28, 29, 30	26, 27, 28, 29, 30	
	Female	51, 52, 53, 54, 55, 56, 57, 58, 59, 60	51, 52, 53, 54, 55, 56, 57, 58, 59, 60	51, 52, 53, 54, 55, 56, 57, 58, 59, 60	51, 52, 53, 54, 55, 56, 57, 58, 59, 60	56, 57, 58, 59, 60	56, 57, 58, 59, 60	

a) Animal number.

Addendum 2-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	50	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	250	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	1,000	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	0
		35	0	0
		36	0	0
		37	0	+1
		38	0	0
		39	0	0
		40	0	0
	50	41	0	0
		42	0	0
		43	0	0
		44	0	0
		45	0	0
	250	46	0	0
		47	0	0
		48	0	0
		49	0	0
		50	0	0
	1,000	51	0	0
		52	0	+1
		53	0	+1
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	0

Addendum 2-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	+1
		2	0	0
		3	0	+1
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	+1
		10	0	0
	50	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	250	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	1,000	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-4 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	0
		35	0	0
		36	0	0
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	50	41	0	0
		42	0	0
		43	0	0
		44	0	0
		45	0	0
	250	46	0	0
		47	0	0
		48	0	0
		49	0	0
		50	0	0
	1,000	51	0	0
		52	0	0
		53	0	0
		54	0	0
		55	0	0
		56	0	0
		57	0	0
		58	0	0
		59	0	0
		60	0	+1

Addendum 2-5 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	50	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	250	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	1,000	21	0	0
		22	0	0
		23	0	0
		24	0	0
		25	0	0
		26	0	0
		27	0	0
		28	0	0
		29	0	0
		30	0	0

Addendum 2-6 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	0
		35	0	0
		36	0	0
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	50	41	0	0
		42	0	0
		43	0	0
		44	0	0
		45	0	0
	250	46	0	0
		47	0	0
		48	0	0
		49	0	0
		50	0	0
	1,000	51	0	0
		52	0	0
		53	0	+1
		54	0	+1
		55	0	0
		56	0	0
		57	0	0
		58	0	+1
		59	0	0
		60	0	+1

Addendum 2-7 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	+1
	50	11	0	+1
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	250	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	1,000	21	0	0
		22	0	0
		23	0	+1
		24	0	0
		25	0	0
		26	0	0
		27	0	+1
		28	0	0
		29	0	0
		30	0	0

Addendum 2-8 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	+1
		34	0	0
		35	0	+1
		36	0	0
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	50	41	0	0
		42	0	+1
		43	0	+1
		44	0	0
		45	0	0
	250	46	0	0
		47	0	0
		48	0	0
		49	0	+1
		50	0	0
	1,000	51	0	0
		52	0	0
		53	0	+1
		54	0	+1
		55	0	0
		56	0	0
		57	0	0
		58	0	+1
		59	0	0
		60	0	+1

Addendum 2-9 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	1	0	0
		2	0	0
		3	0	0
		4	0	0
		5	0	0
		6	0	0
		7	0	0
		8	0	0
		9	0	0
		10	0	0
	50	11	0	0
		12	0	0
		13	0	0
		14	0	0
		15	0	0
	250	16	0	0
		17	0	0
		18	0	0
		19	0	0
		20	0	0
	1,000	21	0	0
		22	0	0
		23	0	0
		24	-1	0
		25	0	0
		26	0	+1
		27	0	+1
		28	0	0
		29	0	0
		30	0	0

Addendum 2-10 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	31	0	0
		32	0	0
		33	0	0
		34	0	0
		35	0	0
		36	0	0
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	50	41	0	0
		42	0	0
		43	0	0
		44	0	0
		45	0	0
	250	46	0	+1
		47	0	0
		48	0	0
		49	0	+1
		50	0	0
	1,000	51	0	0
		52	0	0
		53	0	0
		54	0	+1
		55	0	0
		56	0	0
		57	0	0
		58	0	+1
		59	0	0
		60	0	+1

Addendum 2-11 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	6	0	0
		7	0	0
		8	0	+1
		9	0	0
		10	0	+1
	1,000	26	0	0
		27	0	+1
		28	0	0
		29	0	0
		30	0	0

Addendum 2-12 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	36	0	0
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	1,000	56	0	0
		57	0	+1
		58	0	0
		59	0	0
		60	0	+1

Addendum 2-13 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Male	Vehicle control	6	0	0
		7	0	0
		8	0	+1
		9	0	0
		10	0	+1
	1,000	26	0	0
		27	0	+1
		28	0	0
		29	0	0
		30	0	0

Addendum 2-14 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Removal from cage	
			Ease of removal	Vocalization
Female	Vehicle control	36	0	0
		37	0	0
		38	0	0
		39	0	0
		40	0	0
	1,000	56	0	0
		57	0	0
		58	0	+1
		59	0	0
		60	0	0

Addendum 2-15 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	*Handling observations*						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	50	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	250	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	1,000	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-16 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	50	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	250	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	1,000	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-17 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	50	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	250	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	1,000	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-18 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	50	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	250	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	1,000	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-19 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	50	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	250	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	1,000	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-20 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	50	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	250	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	1,000	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-21 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	50	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	250	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	1,000	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-22 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	50	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	250	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	1,000	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-23 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	*Handling observations*						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	1	0	-	-	-	-	-	-
		2	0	-	-	-	-	-	-
		3	0	-	-	-	-	-	-
		4	0	-	-	-	-	-	-
		5	0	-	-	-	-	-	-
		6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	50	11	0	-	-	-	-	-	-
		12	0	-	-	-	-	-	-
		13	0	-	-	-	-	-	-
		14	0	-	-	-	-	-	-
		15	0	-	-	-	-	-	-
	250	16	0	-	-	-	-	-	-
		17	0	-	-	-	-	-	-
		18	0	-	-	-	-	-	-
		19	0	-	-	-	-	-	-
		20	0	-	-	-	-	-	-
	1,000	21	0	-	-	-	-	-	-
		22	0	-	-	-	-	-	-
		23	0	-	-	-	-	-	-
		24	0	-	-	-	-	-	-
		25	0	-	-	-	-	-	-
		26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-24 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	31	0	-	-	-	-	-	-
		32	0	-	-	-	-	-	-
		33	0	-	-	-	-	-	-
		34	0	-	-	-	-	-	-
		35	0	-	-	-	-	-	-
		36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	50	41	0	-	-	-	-	-	-
		42	0	-	-	-	-	-	-
		43	0	-	-	-	-	-	-
		44	0	-	-	-	-	-	-
		45	0	-	-	-	-	-	-
	250	46	0	-	-	-	-	-	-
		47	0	-	-	-	-	-	-
		48	0	-	-	-	-	-	-
		49	0	-	-	-	-	-	-
		50	0	-	-	-	-	-	-
	1,000	51	0	-	-	-	-	-	-
		52	0	-	-	-	-	-	-
		53	0	-	-	-	-	-	-
		54	0	-	-	-	-	-	-
		55	0	-	-	-	-	-	-
		56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-25 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	1,000	26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-26 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	1,000	56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-27 *Twenty-eight-day repeated-dose oral toxicity study in rats* B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Male	Vehicle control	6	0	-	-	-	-	-	-
		7	0	-	-	-	-	-	-
		8	0	-	-	-	-	-	-
		9	0	-	-	-	-	-	-
		10	0	-	-	-	-	-	-
	1,000	26	0	-	-	-	-	-	-
		27	0	-	-	-	-	-	-
		28	0	-	-	-	-	-	-
		29	0	-	-	-	-	-	-
		30	0	-	-	-	-	-	-

Addendum 2-28 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations						
			Muscle tone	Subnormal temperature	Piloerection	Staining hair	Unkempt hair	Paleness	Reddening
Female	Vehicle control	36	0	-	-	-	-	-	-
		37	0	-	-	-	-	-	-
		38	0	-	-	-	-	-	-
		39	0	-	-	-	-	-	-
		40	0	-	-	-	-	-	-
	1,000	56	0	-	-	-	-	-	-
		57	0	-	-	-	-	-	-
		58	0	-	-	-	-	-	-
		59	0	-	-	-	-	-	-
		60	0	-	-	-	-	-	-

Addendum 2-29 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	50	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	250	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	1,000	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-30 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	*Handling observations*					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	50	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	250	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	1,000	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-31 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	50	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	250	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	1,000	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-32 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	50	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	250	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	1,000	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-33 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	50	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	250	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	1,000	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-34 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	50	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	250	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	1,000	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-35 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	50	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	250	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	1,000	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-36 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	50	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	250	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	1,000	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-37 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	1	-	-	-	0	-	-
		2	-	-	-	0	-	-
		3	-	-	-	0	-	-
		4	-	-	-	0	-	-
		5	-	-	-	0	-	-
		6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	50	11	-	-	-	0	-	-
		12	-	-	-	0	-	-
		13	-	-	-	0	-	-
		14	-	-	-	0	-	-
		15	-	-	-	0	-	-
	250	16	-	-	-	0	-	-
		17	-	-	-	0	-	-
		18	-	-	-	0	-	-
		19	-	-	-	0	-	-
		20	-	-	-	0	-	-
	1,000	21	-	-	-	0	-	-
		22	-	-	-	0	-	-
		23	-	-	-	0	-	-
		24	-	-	-	0	-	-
		25	-	-	-	0	-	-
		26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-38 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	31	-	-	-	0	-	-
		32	-	-	-	0	-	-
		33	-	-	-	0	-	-
		34	-	-	-	0	-	-
		35	-	-	-	0	-	-
		36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	50	41	-	-	-	0	-	-
		42	-	-	-	0	-	-
		43	-	-	-	0	-	-
		44	-	-	-	0	-	-
		45	-	-	-	0	-	-
	250	46	-	-	-	0	-	-
		47	-	-	-	0	-	-
		48	-	-	-	0	-	-
		49	-	-	-	0	-	-
		50	-	-	-	0	-	-
	1,000	51	-	-	-	0	-	-
		52	-	-	-	0	-	-
		53	-	-	-	0	-	-
		54	-	-	-	0	-	-
		55	-	-	-	0	-	-
		56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-39 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	*Handling observations*					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	1,000	26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-40 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	1,000	56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-41 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Male	Vehicle control	6	-	-	-	0	-	-
		7	-	-	-	0	-	-
		8	-	-	-	0	-	-
		9	-	-	-	0	-	-
		10	-	-	-	0	-	-
	1,000	26	-	-	-	0	-	-
		27	-	-	-	0	-	-
		28	-	-	-	0	-	-
		29	-	-	-	0	-	-
		30	-	-	-	0	-	-

Addendum 2-42 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Handling observations					
			Cyanosis	Lacrimation	Exophthalmos	Pupillary size	Salivation	Secretion
Female	Vehicle control	36	-	-	-	0	-	-
		37	-	-	-	0	-	-
		38	-	-	-	0	-	-
		39	-	-	-	0	-	-
		40	-	-	-	0	-	-
	1,000	56	-	-	-	0	-	-
		57	-	-	-	0	-	-
		58	-	-	-	0	-	-
		59	-	-	-	0	-	-
		60	-	-	-	0	-	-

Addendum 2-43 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	50	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	+1	0	-	-
		20	0	0	0	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-44 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	+1	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-45 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	50	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	+1	0	-	-
		19	0	+1	0	-	-
		20	0	0	0	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	-1	0	-	-
		30	0	0	0	-	-

Addendum 2-46 *Twenty-eight-day repeated-dose oral toxicity study in rats* B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena: Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-47 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	+1	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	50	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	+1	0	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	+1	0	-	-
		19	0	0	0	-	-
		20	0	-1	0	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-48 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	+1	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	+1	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-49 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	50	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-50 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	+1	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	+1	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	+1	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	+1	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-51 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	50	11	0	0	0	-	-
		12	0	0	0	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	0	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	-1	0	-	-
		24	0	0	0	-	-
		25	0	0	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-52 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	+1	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	+1	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-53 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	1,000	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-54 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	36	0	0	0	-	-
		37	0	+1	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	1,000	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	+1	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-55 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Male	Vehicle control	6	0	0	0	-	-
		7	0	0	0	-	-
		8	0	+1	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	1,000	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-56 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Posture	Motor activity	Respiration	Lid closure	Gait
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	1,000	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	+1	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-57 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	1	-	-
		2	0	0	1	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	2	1	-	-
		8	0	1	3	-	-
		9	0	0	5	-	-
		10	0	0	3	-	-
	50	11	0	0	9	-	-
		12	0	0	7	-	-
		13	0	0	0	-	-
		14	0	0	2	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	3	2	-	-
		18	0	1	0	-	-
		19	0	0	4	-	-
		20	0	1	0	-	-
	1,000	21	0	0	7	-	-
		22	0	0	0	-	-
		23	0	0	2	-	-
		24	0	0	0	-	-
		25	0	0	1	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	6	-	-
		29	0	1	3	-	-
		30	0	0	0	-	-

Addendum 2-58 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Predosing)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	1	-	-
		32	0	0	0	-	-
		33	0	0	1	-	-
		34	0	0	1	-	-
		35	0	0	1	-	-
		36	0	0	0	-	-
		37	0	0	1	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	0	12	-	-
		43	0	0	11	-	-
		44	0	0	0	-	-
		45	0	0	1	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	3	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	3	1	-	-

Addendum 2-59 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	1	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	3	-	-
		5	0	0	0	-	-
		6	0	0	1	-	-
		7	0	1	0	-	-
		8	0	1	0	-	-
		9	0	0	3	-	-
		10	0	0	1	-	-
	50	11	0	3	0	-	-
		12	0	0	3	-	-
		13	0	0	0	-	-
		14	0	0	1	-	-
		15	0	0	0	-	-
	250	16	0	0	3	-	-
		17	0	2	1	-	-
		18	0	0	1	-	-
		19	0	0	4	-	-
		20	0	0	1	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	0	-	-
		24	0	0	0	-	-
		25	0	1	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	2	-	-
		29	0	0	1	-	-
		30	0	0	0	-	-

Addendum 2-60 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	2	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	2	6	-	-
		43	0	0	4	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	7	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-61 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	0	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	0	-	-
		7	0	0	3	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	50	11	0	0	3	-	-
		12	0	0	2	-	-
		13	0	0	1	-	-
		14	0	0	0	-	-
		15	0	0	2	-	-
	250	16	0	0	0	-	-
		17	0	2	0	-	-
		18	0	0	0	-	-
		19	0	0	3	-	-
		20	0	0	2	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	1	-	-
		24	0	0	0	-	-
		25	0	1	1	-	-
		26	0	0	0	-	-
		27	0	0	1	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	1	-	-

Addendum 2-62 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena: Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	4	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	0	6	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	7	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-63 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	1	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	3	-	-
		7	0	0	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	1	-	-
	50	11	0	1	2	-	-
		12	0	0	1	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	2	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	1	1	-	-
		24	0	0	1	-	-
		25	0	3	0	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	1	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-64 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 3)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	2	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	3	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-65 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	1	0	0	5	-	-
		2	0	0	0	-	-
		3	0	0	0	-	-
		4	0	0	0	-	-
		5	0	0	0	-	-
		6	0	0	1	-	-
		7	0	0	1	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	50	11	0	0	0	-	-
		12	0	0	1	-	-
		13	0	0	0	-	-
		14	0	0	0	-	-
		15	0	0	0	-	-
	250	16	0	0	0	-	-
		17	0	2	0	-	-
		18	0	0	0	-	-
		19	0	0	0	-	-
		20	0	0	0	-	-
	1,000	21	0	0	0	-	-
		22	0	0	0	-	-
		23	0	0	1	-	-
		24	0	0	0	-	-
		25	0	1	1	-	-
		26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-66 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena: Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	31	0	0	0	-	-
		32	0	0	0	-	-
		33	0	0	0	-	-
		34	0	0	0	-	-
		35	0	0	0	-	-
		36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	50	41	0	0	0	-	-
		42	0	0	0	-	-
		43	0	0	0	-	-
		44	0	0	0	-	-
		45	0	0	0	-	-
	250	46	0	0	0	-	-
		47	0	0	0	-	-
		48	0	0	0	-	-
		49	0	0	0	-	-
		50	0	0	0	-	-
	1,000	51	0	0	0	-	-
		52	0	0	0	-	-
		53	0	0	0	-	-
		54	0	0	0	-	-
		55	0	0	0	-	-
		56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	1	-	-
		60	0	0	0	-	-

Addendum 2-67 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	6	0	0	3	-	-
		7	0	1	0	-	-
		8	0	0	0	-	-
		9	0	0	0	-	-
		10	0	0	0	-	-
	1,000	26	0	0	0	-	-
		27	0	0	1	-	-
		28	0	0	1	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-68 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 1)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	1,000	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 2-69 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp.group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Male	Vehicle control	6	0	0	7	-	-
		7	0	0	0	-	-
		8	0	0	8	-	-
		9	0	0	0	-	-
		10	0	0	2	-	-
	1,000	26	0	0	0	-	-
		27	0	0	0	-	-
		28	0	0	0	-	-
		29	0	0	0	-	-
		30	0	0	0	-	-

Addendum 2-70 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Detailed clinical observations of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Observations in arena				
			Tremor/twitch/ convulsion	Defecation (count/min)	Urination (count/min)	Stereotypic behavior	Abnormal behavior
Female	Vehicle control	36	0	0	0	-	-
		37	0	0	0	-	-
		38	0	0	0	-	-
		39	0	0	0	-	-
		40	0	0	0	-	-
	1,000	56	0	0	0	-	-
		57	0	0	0	-	-
		58	0	0	0	-	-
		59	0	0	0	-	-
		60	0	0	0	-	-

Addendum 3-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Reflex of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Sensorimotor function				
			Approach contact/ touch response	Pinna response	Pain response (tail pinch)	Pupillary reflex	Air righting reflex
Male	Vehicle control	1	0	0	0	+	+
		2	0	0	0	+	+
		3	0	0	0	+	+
		4	0	0	0	+	+
		5	0	0	0	+	+
		6	0	0	0	+	+
		7	0	0	0	+	+
		8	0	0	0	+	+
		9	0	0	0	+	+
		10	0	0	0	+	+
	50	11	0	0	0	+	+
		12	0	0	0	+	+
		13	0	0	0	+	+
		14	0	0	0	+	+
		15	0	0	0	+	+
	250	16	0	0	0	+	+
		17	0	0	0	+	+
		18	0	0	0	+	+
		19	0	0	0	+	+
		20	0	0	0	+	+
	1,000	21	0	0	0	+	+
		22	0	0	0	+	+
		23	0	0	0	+	+
		24	0	0	0	+	+
		25	0	0	0	+	+
		26	0	0	0	+	+
		27	0	0	0	+	+
		28	0	0	0	+	+
		29	0	0	0	+	+
		30	0	0	0	+	+

Addendum 3-2 *Twenty-eight-day repeated-dose oral toxicity study in rats* B11-0897

Reflex of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Sensorimotor function				
			Approach contact/ touch response	Pinna response	Pain response (tail pinch)	Pupillary reflex	Air righting reflex
Female	Vehicle control	31	0	0	0	+	+
		32	0	0	0	+	+
		33	0	0	0	+	+
		34	0	0	0	+	+
		35	0	0	0	+	+
		36	0	0	0	+	+
		37	0	0	0	+	+
		38	0	0	0	+	+
		39	0	0	0	+	+
		40	0	0	0	+	+
	50	41	0	0	0	+	+
		42	0	0	0	+	+
		43	0	0	0	+	+
		44	0	0	0	+	+
		45	0	0	0	+	+
	250	46	0	0	0	+	+
		47	0	0	0	+	+
		48	0	0	0	+	+
		49	0	0	0	+	+
		50	0	0	0	+	+
	1,000	51	0	0	0	+	+
		52	0	0	0	+	+
		53	0	0	0	+	+
		54	0	0	0	+	+
		55	0	0	0	+	+
		56	0	0	0	+	+
		57	0	0	0	+	+
		58	0	0	0	+	+
		59	0	0	0	+	+
		60	0	0	0	+	+

Addendum 4-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Grip strength of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Forelimb (g)			Hindlimb (g)		
			Trial 1	Trial 2	Mean	Trial 1	Trial 2	Mean
Male	Vehicle control	1	436	399	418	404	369	387
		2	437	415	426	429	350	390
		3	425	412	419	410	376	393
		4	434	406	420	360	405	383
		5	462	388	425	464	468	466
		6	475	393	434	386	488	437
		7	423	397	410	416	426	421
		8	371	355	363	376	405	391
		9	488	500	494	407	457	432
		10	458	448	453	404	416	410
	50	11	436	428	432	391	419	405
		12	388	357	373	363	407	385
		13	396	378	387	419	427	423
		14	367	388	378	352	361	357
		15	436	450	443	336	425	381
	250	16	384	363	374	397	388	393
		17	423	382	403	458	404	431
		18	469	382	426	336	415	376
		19	426	386	406	458	439	449
		20	382	373	378	364	346	355
	1,000	21	477	405	441	372	375	374
		22	411	368	390	376	353	365
		23	449	454	452	496	428	462
		24	446	374	410	429	425	427
		25	380	451	416	372	431	402
		26	416	451	434	398	374	386
		27	406	362	384	399	406	403
		28	455	353	404	466	453	460
		29	401	427	414	414	399	407
		30	468	485	477	397	446	422

Addendum 4-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Grip strength of individual animals (week 4)

Sex	Exp.group (mg/kg/day)	Animal No.	Forelimb (g)			Hindlimb (g)		
			Trial 1	Trial 2	Mean	Trial 1	Trial 2	Mean
Female	Vehicle control	31	316	399	358	389	319	354
		32	343	380	362	406	323	365
		33	314	329	322	381	328	355
		34	356	315	336	416	349	383
		35	377	322	350	334	320	327
		36	317	294	306	385	320	353
		37	313	356	335	388	360	374
		38	380	325	353	318	332	325
		39	387	331	359	339	332	336
		40	393	330	362	411	367	389
	50	41	323	321	322	352	382	367
		42	345	324	335	384	397	391
		43	297	381	339	366	362	364
		44	341	385	363	357	400	379
		45	318	341	330	386	379	383
	250	46	383	350	367	328	323	326
		47	367	357	362	361	407	384
		48	396	348	372	366	350	358
		49	340	330	335	379	339	359
		50	316	391	354	381	357	369
	1,000	51	362	399	381	388	396	392
		52	389	323	356	334	324	329
		53	270	343	307	361	308	335
		54	373	362	368	383	415	399
		55	343	327	335	374	368	371
		56	321	391	356	336	407	372
		57	377	345	361	346	345	346
		58	344	325	335	365	389	377
		59	305	323	314	428	359	394
		60	375	319	347	353	337	345

Addendum 5-1 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Motor activity of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Interval (min)						
			0-10	10-20	20-30	30-40	40-50	50-60	Total
Male	Vehicle control	1	224	126	72	17	4	3	446
		2	216	69	73	18	1	84	461
		3	153	130	11	0	0	1	295
		4	182	69	23	71	0	3	348
		5	215	200	187	110	65	6	783
		6	181	140	39	3	0	0	363
		7	251	143	86	52	2	0	534
		8	202	173	80	38	83	23	599
		9	224	48	45	58	138	105	618
		10	198	166	118	28	137	25	672
	50	11	267	135	68	16	74	91	651
		12	155	52	0	1	0	0	208
		13	212	71	3	69	17	31	403
		14	295	47	73	26	1	4	446
		15	237	98	60	23	0	0	418
	250	16	292	140	11	103	0	0	546
		17	45	184	119	6	71	20	445
		18	167	116	6	1	35	15	340
		19	324	120	78	114	83	92	811
		20	147	169	101	29	59	64	569
	1,000	21	274	49	124	23	5	0	475
		22	214	147	82	68	6	66	583
		23	181	129	53	32	32	0	427
		24	270	129	53	0	0	0	452
		25	119	84	28	8	8	6	253
		26	299	126	61	9	0	0	495
		27	197	67	22	0	0	0	286
		28	274	117	73	29	129	6	628
		29	261	236	192	135	60	62	946
		30	219	107	13	89	0	34	462

Addendum 5-2 *Twenty-eight-day repeated-dose oral toxicity study in rats* B11-0897

Motor activity of individual animals (week 4)

Sex	Exp. group (mg/kg/day)	Animal No.	Interval (min)						
			0-10	10-20	20-30	30-40	40-50	50-60	Total
Female	Vehicle control	31	223	185	127	116	148	190	989
		32	212	144	98	49	0	0	503
		33	219	189	168	0	88	31	695
		34	302	360	286	174	185	1	1308
		35	313	286	264	296	410	302	1871
		36	215	125	31	135	13	1	520
		37	234	35	37	2	0	75	383
		38	132	111	31	0	48	55	377
		39	204	152	70	52	46	0	524
		40	194	114	25	19	4	0	356
	50	41	247	164	164	106	50	59	790
		42	141	32	169	86	151	42	621
		43	111	103	63	67	57	44	445
		44	215	67	81	35	0	0	398
		45	183	85	74	11	0	0	353
	250	46	353	206	130	10	2	94	795
		47	166	32	0	2	87	13	300
		48	216	126	79	57	1	2	481
		49	270	132	13	0	52	16	483
		50	207	5	0	3	147	32	394
	1,000	51	185	87	7	47	0	31	357
		52	237	17	30	112	6	1	403
		53	236	55	96	6	1	0	394
		54	255	120	64	43	0	4	486
		55	214	116	96	2	0	0	428
		56	243	80	1	25	18	19	386
		57	156	51	6	0	2	119	334
		58	215	131	0	13	144	143	646
		59	241	98	29	84	18	47	517
		60	244	57	64	12	0	0	377

Addendum 5-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Motor activity of individual animals (Recovery week 2)

Sex	Exp. group (mg/kg/day)	Animal No.	Interval (min)						
			0-10	10-20	20-30	30-40	40-50	50-60	Total
Female	Vehicle control	36	207	99	68	10	0	0	384
		37	113	2	2	4	23	21	165
		38	115	91	24	21	7	50	308
		39	189	100	133	105	81	62	670
		40	169	151	38	17	11	1	387
	1,000	56	220	131	55	42	60	41	549
		57	162	12	0	43	113	56	386
		58	223	175	159	113	19	0	689
		59	178	73	42	90	69	0	452
		60	201	104	18	133	106	8	570

Addendum 6-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-1	1	3	8	12	17	21	26	28 (days)
Male	Vehicle control	1	135.9	142.6	161.7	204.4	234.2	268.1	295.0	334.6	339.7
		2	129.8	137.3	151.5	195.2	230.2	271.6	298.5	327.4	333.6
		3	119.6	125.1	139.0	171.1	197.6	234.8	265.6	297.9	307.9
		4	124.4	131.6	146.6	189.7	222.5	263.5	289.2	319.0	327.8
		5	122.9	130.9	147.9	186.6	210.5	246.6	271.1	293.6	304.7
		6	134.8	140.2	157.5	205.1	237.1	274.7	303.1	332.6	342.4
		7	119.4	123.0	136.9	172.9	202.2	233.9	263.8	287.9	298.0
		8	123.6	131.5	150.2	189.0	221.7	261.9	291.5	315.3	323.6
		9	121.7	126.2	140.9	183.4	215.6	263.8	293.3	329.1	340.8
		10	128.6	134.4	148.8	188.1	221.5	259.1	288.4	311.8	321.0
	50	11	130.3	137.4	157.5	206.5	245.2	291.5	324.2	364.0	368.6
		12	120.9	127.9	142.7	180.5	213.1	245.6	271.2	304.2	308.1
		13	124.8	130.0	143.5	178.5	213.8	256.6	288.7	328.2	334.3
		14	134.2	139.4	155.6	195.9	228.2	264.3	298.7	327.4	336.0
		15	120.6	127.0	139.9	179.2	214.0	250.5	279.7	311.7	319.5
	250	16	134.0	137.2	156.2	206.2	248.6	288.1	321.5	358.6	367.0
		17	120.7	126.9	143.4	188.6	223.7	267.4	299.1	334.3	346.2
		18	137.3	144.2	159.8	210.2	245.6	287.7	318.0	350.0	357.4
		19	124.7	131.4	148.4	197.0	229.4	268.1	299.4	332.2	338.7
		20	123.0	128.6	145.7	194.5	229.0	264.7	294.3	328.2	336.9
	1,000	21	125.4	132.4	149.4	185.5	222.2	257.0	283.4	308.6	318.7
		22	119.6	125.1	139.1	181.4	214.4	261.8	291.4	335.8	344.0
		23	130.6	137.8	157.3	213.3	253.7	298.3	328.9	363.8	374.6
		24	121.8	125.4	138.6	180.0	213.3	254.9	283.3	314.0	323.8
		25	139.6	145.8	168.3	227.4	266.6	313.5	350.1	383.7	397.3
		26	117.0	121.3	132.3	168.6	201.0	239.5	271.5	299.5	312.8
		27	129.5	135.8	153.9	196.2	235.3	276.6	305.5	335.2	341.9
		28	122.9	130.1	145.0	190.5	222.3	262.6	295.8	328.3	340.3
		29	124.9	132.8	146.7	188.7	218.3	259.4	296.5	331.6	335.2
		30	135.2	140.7	156.5	198.5	235.3	286.4	317.7	362.0	371.1

Addendum 6-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period								
			-1	1	3	8	12	17	21	26	28 (days)
Female	Vehicle control	31	106.0	111.3	120.6	149.0	166.9	190.5	209.7	220.5	227.8
		32	108.0	113.7	128.2	154.4	173.0	200.0	216.9	239.8	230.3
		33	107.2	113.1	125.0	143.2	159.2	173.4	188.0	207.3	200.4
		34	110.0	116.5	129.2	157.1	174.7	187.4	201.7	211.3	215.0
		35	114.4	123.2	137.1	170.1	185.7	205.0	224.0	243.6	242.5
		36	107.2	110.4	122.5	146.6	153.9	167.5	169.1	180.4	194.8
		37	111.4	115.3	129.1	155.8	167.0	184.5	195.9	208.1	221.4
		38	109.2	116.9	129.1	155.8	171.2	186.4	195.1	211.3	213.2
		39	102.1	108.2	116.3	133.9	142.6	153.1	158.4	177.9	171.5
		40	111.8	118.6	128.6	157.4	178.0	196.6	210.2	231.2	239.6
	50	41	105.6	112.0	122.6	146.9	160.4	184.1	198.7	214.8	209.6
		42	106.5	113.0	123.1	149.6	166.4	181.7	190.3	207.9	211.4
		43	108.3	110.6	122.8	150.3	168.3	180.1	196.2	211.5	219.0
		44	112.0	117.3	129.1	150.8	164.4	183.0	195.3	214.1	211.2
		45	111.0	116.7	125.9	139.7	152.9	166.1	178.2	194.9	190.7
	250	46	113.9	117.5	130.4	150.4	167.5	171.7	181.3	203.1	201.3
		47	110.7	115.5	124.4	148.2	164.8	184.3	200.9	213.8	213.6
		48	107.7	113.0	125.5	152.4	170.2	192.5	202.7	222.3	227.3
		49	106.4	113.6	122.3	150.2	163.1	184.8	205.0	226.9	228.4
		50	108.4	114.2	128.9	159.5	176.9	199.4	217.8	230.4	239.6
	1,000	51	105.6	110.1	121.3	145.2	159.6	174.9	186.6	200.0	205.5
		52	108.3	116.6	133.4	156.9	174.1	182.9	197.2	217.8	209.2
		53	109.3	114.1	130.1	151.2	161.6	170.6	186.0	206.6	203.0
		54	107.1	112.1	124.6	153.8	168.7	185.0	200.6	214.3	224.9
		55	112.5	117.4	127.5	156.1	174.0	192.1	213.7	229.2	237.7
		56	107.8	114.3	127.0	146.6	162.5	169.4	183.9	207.4	210.3
		57	102.3	105.3	115.6	138.0	147.4	160.0	170.0	188.8	182.6
		58	112.8	118.2	130.9	147.1	160.8	184.1	197.1	221.4	217.7
		59	110.3	115.4	128.5	152.6	168.4	199.1	209.7	224.0	218.0
		60	107.3	109.5	119.2	143.4	154.9	169.9	182.3	203.8	200.8

Addendum 6-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Body weights of individual animals(g)

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 1	5	10	14 (days)
Male	Vehicle control	6	344.6	362.8	387.7	403.8
		7	300.9	319.6	345.8	358.2
		8	328.6	344.4	378.6	398.3
		9	346.2	364.2	394.6	417.3
		10	322.5	340.0	360.6	375.7
	1,000	26	312.0	325.2	346.3	357.2
		27	341.5	358.1	381.2	396.3
		28	340.6	359.1	383.7	396.4
		29	340.6	356.1	385.3	401.9
		30	378.4	397.0	428.1	452.3
Female	Vehicle control	36	195.2	199.1	211.7	217.9
		37	222.5	233.4	242.6	253.2
		38	219.4	232.3	243.2	253.7
		39	179.8	186.5	198.8	205.4
		40	236.2	245.7	261.2	268.1
	1,000	56	210.7	220.9	241.0	247.1
		57	169.6	201.4	222.1	228.5
		58	224.4	230.6	244.7	252.1
		59	227.4	236.7	245.4	253.5
		60	209.4	216.6	228.8	231.1

Addendum 7-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes of individual animals(g/rat/day)

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period 1	3	8	15	22	28 (days)
Male	Vehicle control	1	18.1	21.2	22.8	22.2	23.2	24.2
		2	18.9	19.0	22.2	23.9	25.0	24.8
		3	16.4	18.1	19.2	20.8	23.4	24.3
		4	16.1	18.0	20.8	22.7	23.9	22.8
		5	15.9	20.0	21.5	22.3	23.6	24.4
		6	17.2	20.0	23.4	24.1	25.3	25.7
		7	14.3	17.8	18.6	20.2	21.7	22.2
		8	16.8	19.2	21.0	22.8	25.4	24.5
		9	14.1	17.3	19.8	22.9	25.4	26.1
		10	17.8	20.1	22.2	24.3	24.9	24.5
	50	11	19.4	20.2	23.3	24.8	26.7	27.5
		12	17.7	18.0	20.0	21.6	22.3	23.0
		13	15.4	17.3	19.7	22.4	24.5	25.5
		14	17.5	19.6	22.1	23.2	25.1	24.1
		15	15.1	17.3	20.2	22.9	24.7	24.8
	250	16	16.9	19.8	23.3	25.3	25.2	27.1
		17	16.8	19.2	22.0	24.5	24.9	26.6
		18	18.6	20.4	23.4	24.7	27.3	28.1
		19	18.4	20.6	24.1	24.9	26.0	26.6
		20	16.4	19.4	23.9	24.8	25.2	25.9
	1,000	21	17.5	18.4	19.8	22.1	23.3	22.4
		22	15.2	17.6	20.7	23.0	26.2	27.9
		23	17.7	20.6	24.4	26.1	28.3	28.0
		24	15.1	16.9	20.3	21.4	24.2	25.0
		25	19.2	21.6	26.8	28.2	30.0	30.4
		26	14.3	16.0	19.0	21.3	23.9	24.3
		27	16.7	21.2	21.9	23.8	25.6	25.2
		28	16.1	17.7	21.8	23.3	24.4	25.0
		29	18.5	17.8	21.1	22.4	25.3	25.7
		30	18.7	20.9	23.0	27.2	31.0	33.3

Addendum 7-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Food intakes of individual animals(g/rat/day)

811-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Administration period 1	3	8	15	22	28 (days)
Female	Vehicle control	31	13.4	14.9	17.1	16.9	18.2	18.2
		32	15.4	16.7	17.5	18.7	19.7	19.6
		33	15.0	15.9	16.6	17.2	17.9	17.5
		34	15.1	17.2	17.5	17.9	18.8	18.2
		35	16.1	18.7	19.7	18.8	20.6	19.8
		36	13.3	15.1	15.9	15.0	14.2	15.3
		37	13.6	16.4	17.0	16.4	16.6	18.1
		38	14.5	16.9	18.0	16.8	17.6	17.6
		39	12.7	13.5	14.7	14.8	14.7	14.4
		40	15.2	17.8	18.4	18.5	19.6	20.0
	50	41	15.2	16.0	16.6	17.0	17.4	16.7
		42	13.6	14.9	16.2	16.0	15.9	15.6
		43	12.9	14.8	17.0	16.8	17.7	17.4
		44	15.6	15.4	17.3	17.0	17.9	17.9
		45	15.5	15.3	14.7	15.3	15.7	16.2
	250	46	14.1	16.7	16.1	15.7	16.4	16.6
		47	14.2	16.2	16.1	16.2	17.6	16.9
		48	14.7	16.0	16.9	17.9	19.2	17.8
		49	14.5	15.0	17.0	17.8	19.0	18.4
		50	15.9	17.9	18.6	17.6	18.8	20.3
	1,000	51	13.4	14.2	16.2	15.8	16.0	17.4
		52	15.0	17.2	17.6	16.4	18.0	17.5
		53	14.0	16.3	17.3	16.6	17.4	16.7
		54	13.1	15.5	17.6	17.7	17.3	18.0
		55	14.4	15.3	17.9	18.7	19.7	20.5
		56	15.4	16.7	17.3	16.8	17.4	18.5
		57	12.1	15.0	16.8	15.8	16.4	15.8
		58	13.5	17.3	16.8	17.5	18.2	19.3
		59	14.7	17.3	18.8	18.4	18.4	17.9
		60	11.5	13.4	16.3	16.1	16.6	17.4

Addendum 7-3 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897

Food intakes of individual animals(g/rat/day)

Sex	Exp.group (mg/kg/day)	Animal No.	Recovery period 4	8	14 (days)
Male	Vehicle control	6	25.3	26.2	24.9
		7	22.1	22.8	22.4
		8	24.0	22.6	24.9
		9	24.0	25.8	26.6
		10	21.9	23.9	23.8
	1,000	26	22.8	22.3	21.9
		27	23.0	23.8	23.7
		28	24.0	23.7	23.0
		29	23.3	25.3	24.3
		30	30.7	30.0	28.7
Female	Vehicle control	36	12.6	15.9	16.5
		37	18.1	18.8	18.2
		38	15.9	19.6	19.7
		39	13.1	16.0	16.5
		40	19.1	20.2	19.2
	1,000	56	18.3	19.7	18.6
		57	15.1	16.7	17.8
		58	18.5	18.3	19.0
		59	16.5	16.5	18.5
		60	16.1	18.7	17.4

Addendum 8-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Male	Vehicle control	1	743	117	15.0	43.2	58.1	20.1	34.6	105.1	2.6	16.0	28.7
		2	750	125	15.6	44.9	59.9	20.8	34.6	98.3	2.7	15.8	29.1
		3	724	96	15.1	43.9	60.6	20.9	34.4	104.7	3.1	17.9	28.3
		4	770	79	15.6	45.9	59.6	20.3	34.0	101.9	2.4	25.0	33.9
		5	796	103	15.8	45.9	57.7	19.9	34.5	102.7	2.1	15.3	26.7
		Recovery											
		6	797	104	16.0	47.1	59.1	20.0	33.9	93.7	2.8	21.7	30.7
		7	821	100	15.2	45.0	54.8	18.6	33.9	96.7	1.8	17.4	32.2
		8	853	127	16.0	46.3	54.2	18.8	34.6	100.4	1.7	18.6	35.0
		9	798	160	15.5	45.4	57.0	19.4	34.1	91.2	2.5	17.4	39.7
		10	814	131	16.0	46.0	56.5	19.6	34.7	99.6	2.5	19.0	31.0
	50	11	733	110	14.7	42.5	58.0	20.0	34.5	100.4	2.2	22.6	29.2
		12	762	108	15.9	46.6	61.2	20.9	34.1	113.4	3.1	20.4	36.6
		13	814	100	15.7	46.2	56.7	19.3	34.1	117.8	3.0	16.9	35.6
		14	780	102	15.2	45.6	58.5	19.5	33.3	100.3	2.5	20.0	34.0
		15	735	101	15.1	44.5	60.5	20.6	34.0	98.4	2.3	14.8	26.5
	250	16	769	81	15.0	44.5	57.9	19.6	33.8	106.5	2.9	18.7	35.6
		17	751	166	15.3	45.1	60.1	20.4	34.0	110.8	3.1	19.4	31.2
		18	829	130	16.1	47.6	57.5	19.4	33.7	115.5	2.2	19.5	33.5
		19	811	79	15.6	46.2	56.9	19.2	33.7	124.0	2.6	21.4	31.8
		20	747	100	16.0	47.0	63.0	21.5	34.1	101.1	2.7	23.6	36.8
	1,000	21	720	120	14.7	43.4	60.2	20.4	33.8	99.4	2.9	15.9	31.3
		22	739	126	15.0	43.6	58.9	20.2	34.3	114.9	3.5	18.8	33.3
		23	737	128	15.3	44.5	60.4	20.7	34.3	101.6	2.9	22.1	31.2
		24	779	92	15.3	45.1	57.9	19.6	33.9	106.3	2.9	16.4	26.9
		25	751	97	15.9	46.8	62.3	21.2	34.0	92.2	3.0	15.7	27.6
		Recovery											
		26	882	120	16.9	48.5	55.0	19.2	34.9	105.3	1.4	29.0	43.6
		27	819	101	15.7	46.4	56.6	19.1	33.8	93.6	2.0	20.3	39.7
		28	789	156	15.1	44.3	56.1	19.1	34.1	98.0	1.8	20.7	36.2
		29	828	123	15.4	44.9	54.2	18.5	34.2	105.7	1.7	17.9	30.9
		30	806	108	16.0	46.8	58.1	19.9	34.2	96.4	2.1	16.8	26.8

Addendum 8-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	RBC ($\times 10^4/\mu L$)	WBC ($\times 10^2/\mu L$)	Hb (g/dL)	Ht (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet ($\times 10^4/\mu L$)	Reticulo (%)	P T (sec)	APTT (sec)
Female	Vehicle control	31	738	80	15.3	44.3	60.1	20.8	34.6	101.2	1.7	14.3	19.7
		32	753	104	15.1	43.7	58.0	20.0	34.5	118.0	1.9	14.7	21.7
		33	773	79	15.5	44.5	57.6	20.0	34.8	105.7	1.6	14.0	19.6
		34	786	112	15.3	44.2	56.2	19.4	34.6	109.5	1.9	13.9	20.5
		35	781	108	15.8	45.1	57.8	20.2	34.9	121.5	2.0	13.7	20.7
		Recovery											
		36	827	62	16.3	45.9	55.5	19.7	35.5	120.6	2.1	13.6	24.2
		37	844	71	15.8	44.6	52.8	18.7	35.4	132.5	1.8	13.3	22.1
		38	823	69	15.3	43.7	53.1	18.5	35.0	119.3	1.9	12.8	25.1
		39	780	102	15.3	42.7	54.7	19.6	35.8	128.5	2.1	14.3	23.1
		40	797	51	15.2	42.9	53.9	19.1	35.4	122.5	1.3	13.6	25.2
	50	41	721	125	14.8	42.5	59.0	20.5	34.8	98.4	1.9	14.4	21.0
		42	807	59	15.6	45.4	56.2	19.3	34.4	117.8	1.3	14.0	20.3
		43	770	135	15.3	44.1	57.3	19.9	34.7	105.9	2.0	13.3	25.2
		44	749	88	15.6	43.7	58.3	20.8	35.6	101.2	1.5	13.9	23.3
		45	802	65	15.3	45.1	56.2	19.1	34.0	110.1	1.6	13.2	23.9
	250	46	793	79	15.5	44.5	56.1	19.5	34.8	94.7	1.7	13.4	24.0
		47	780	65	15.4	45.1	57.8	19.7	34.1	103.2	1.7	14.4	21.0
		48	790	142	15.6	45.7	57.8	19.7	34.1	115.9	2.0	14.2	25.5
		49	752	92	15.1	43.7	58.1	20.1	34.6	105.1	2.4	14.8	19.5
		50	765	113	15.8	46.3	60.5	20.7	34.2	103.9	2.6	13.2	21.4
	1,000	51	735	127	14.5	41.6	56.6	19.7	34.8	108.2	2.7	13.2	24.7
		52	770	95	15.3	45.0	58.5	19.9	34.0	113.9	2.0	12.9	18.4
		53	754	99	14.7	41.9	55.6	19.5	35.1	124.4	2.5	12.8	23.0
		54	753	97	15.0	44.1	58.5	19.9	34.1	107.3	2.5	14.1	22.6
		55	720	106	14.8	42.7	59.2	20.5	34.6	109.5	2.2	13.8	19.8
		Recovery											
		56	801	87	15.5	43.5	54.3	19.4	35.7	121.3	1.9	13.8	20.4
		57	803	120	15.4	44.1	54.9	19.2	35.0	145.3	2.5	14.7	22.0
		58	802	60	15.4	42.9	53.5	19.2	35.9	121.0	2.2	14.3	24.2
		59	824	113	15.6	44.0	53.4	18.9	35.4	131.5	1.8	14.0	23.9
		60	760	77	15.5	43.9	57.8	20.4	35.2	117.4	2.4	13.8	25.7

Addendum 8-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%) Neutro	Eosino	Baso	Lymph	Mono	LUC
Male	Vehicle control	1	23.6	1.0	0.3	70.6	3.6	0.9
		2	14.7	0.8	0.3	81.5	1.7	0.9
		3	18.2	0.6	0.3	76.5	3.5	0.9
		4	20.4	1.0	0.3	75.7	1.9	0.6
		5	15.4	1.2	0.2	79.7	2.9	0.5
		Recovery						
		6	21.7	0.7	0.1	71.4	4.5	1.5
		7	20.8	1.0	0.1	75.3	2.4	0.3
		8	10.0	0.7	0.5	85.8	2.5	0.6
		9	15.0	0.7	0.2	81.0	2.0	1.0
		10	13.8	0.4	0.2	82.0	2.3	1.2
	50	11	19.3	0.6	0.4	74.7	3.2	1.8
		12	18.3	1.0	0.2	77.7	2.1	0.7
		13	19.9	0.6	0.2	76.1	2.8	0.4
		14	14.9	1.2	0.4	79.5	3.3	0.8
		15	24.0	1.0	0.2	72.4	1.9	0.5
	250	16	6.1	0.6	0.2	90.0	2.5	0.6
		17	14.4	0.8	0.3	80.8	2.7	1.0
		18	12.2	0.9	0.2	84.1	1.4	1.2
		19	23.1	1.1	0.2	71.4	3.4	0.8
		20	8.5	0.8	0.3	87.0	3.0	0.5
	1,000	21	14.2	1.0	0.2	81.3	2.3	1.1
		22	16.7	1.3	0.4	77.5	3.2	0.9
		23	22.3	1.2	0.3	72.7	3.0	0.5
		24	18.4	1.0	0.1	78.8	1.1	0.6
		25	16.2	1.0	0.2	79.7	2.0	1.0
		Recovery						
		26	15.1	1.0	0.3	79.4	3.4	0.8
		27	9.2	0.8	0.2	86.5	2.5	0.8
		28	8.0	0.6	0.2	88.6	2.0	0.6
		29	7.6	0.6	0.2	89.2	1.7	0.7
		30	14.7	0.6	0.1	80.8	2.8	1.0

Addendum 8-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Hematological data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Differentiation of leukocyte (%)					
			Neutro	Eosino	Baso	Lymph	Mono	LUC
Female	Vehicle control	31	15.4	1.0	0.2	79.9	2.6	0.9
		32	12.4	1.7	0.1	81.4	3.5	0.8
		33	15.4	1.9	0.2	79.2	2.2	1.1
		34	21.9	1.3	0.3	73.7	2.4	0.5
		35	8.4	1.4	0.2	86.6	2.2	1.1
		Recovery						
		36	10.4	1.3	0.1	86.4	1.3	0.5
		37	14.8	1.4	0.1	80.9	2.0	0.7
		38	15.5	0.8	0.1	81.3	1.5	0.8
		39	18.8	1.2	0.1	78.0	1.2	0.7
		40	18.8	2.3	0.3	74.5	3.5	0.7
	50	41	16.4	1.3	0.2	77.4	3.5	1.2
		42	17.1	1.2	0.2	77.9	2.9	0.7
		43	6.9	0.9	0.2	88.1	2.7	1.2
		44	16.2	0.6	0.2	78.5	3.5	1.0
		45	17.2	1.2	0.3	78.1	2.3	0.9
	250	46	22.2	1.8	0.1	72.6	2.5	0.8
		47	18.2	1.7	0.3	76.8	2.4	0.6
		48	23.7	1.0	0.2	71.6	2.3	1.2
		49	12.4	1.4	0.2	82.8	2.0	1.2
		50	10.6	1.1	0.3	84.2	2.7	1.1
	1,000	51	18.7	1.3	0.2	76.0	2.9	0.9
		52	27.0	1.5	0.1	68.4	2.5	0.4
		53	23.8	0.5	0.1	72.5	1.9	1.2
		54	17.0	0.7	0.2	77.9	3.1	1.1
		55	18.4	1.0	0.2	75.8	3.4	1.2
		Recovery						
		56	21.3	1.9	0.1	74.2	1.8	0.8
		57	25.4	1.4	0.1	70.3	1.9	0.9
		58	14.7	0.9	0.2	81.1	2.4	0.6
		59	12.1	1.0	0.3	84.0	1.4	1.2
		60	8.0	1.0	0.2	88.4	1.5	0.8

Addendum 9-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Male	Vehicle control	1	71	22	456	39	0.8	62	34	112	5.6	2.7	0.93
		2	67	22	524	35	0.7	55	57	137	5.7	3.0	1.11
		3	78	27	559	37	0.6	64	81	124	5.5	2.9	1.12
		4	77	28	431	38	0.9	56	55	127	5.5	2.8	1.04
		5	77	29	497	34	0.5	48	74	124	5.7	2.9	1.04
		Recovery											
		6	81	26	250	56	0.8	49	72	154	5.7	2.7	0.90
		7	80	28	324	37	0.9	47	35	141	5.2	2.6	1.00
		8	74	21	304	58	0.9	50	44	152	5.7	2.8	0.97
		9	69	27	309	31	0.6	55	25	141	5.7	2.8	0.97
		10	77	29	289	37	0.7	43	55	142	5.7	2.6	0.84
	50	11	75	21	384	32	0.5	68	73	132	5.6	2.8	1.00
		12	86	24	386	35	0.7	54	47	121	5.6	3.0	1.15
		13	88	28	375	42	1.3	47	47	106	5.8	2.9	1.00
		14	72	24	411	51	0.9	55	63	131	5.9	2.8	0.90
		15	73	20	571	38	0.5	46	49	146	5.7	3.0	1.11
	250	16	74	21	519	69	0.7	52	38	133	5.5	2.8	1.04
		17	74	25	585	32	0.9	49	43	119	5.6	2.8	1.00
		18	99	35	413	35	0.3	57	82	169	5.9	3.0	1.03
		19	92	29	452	30	0.4	46	36	134	5.8	2.9	1.00
		20	81	31	593	52	0.7	54	52	120	5.9	2.9	0.97
	1,000	21	67	23	447	50	0.4	44	38	140	5.4	2.9	1.16
		22	85	25	541	48	0.7	42	77	146	5.5	2.9	1.12
		23	69	28	470	34	0.8	50	84	146	5.5	2.8	1.04
		24	70	25	390	37	0.6	42	40	138	5.2	2.9	1.26
		25	58	21	431	54	0.7	61	78	157	5.8	2.9	1.00
		Recovery											
		26	81	21	413	48	0.9	36	46	139	5.3	2.8	1.12
		27	61	24	377	36	0.7	49	69	138	5.5	2.8	1.04
		28	70	21	283	56	0.4	64	51	153	5.6	2.8	1.00
		29	70	19	237	47	0.6	36	36	158	5.8	2.9	1.00
		30	87	32	293	61	0.7	57	76	135	5.7	2.7	0.90

Addendum 9-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	ChE (IU/L)	γ-GTP (IU/L)	T-Cho (mg/dL)	TG (mg/dL)	Glucose (mg/dL)	T-Protein (g/dL)	Albumin (g/dL)	A/G ratio
Female	Vehicle control	31	85	22	351	331	0.9	67	24	116	5.6	3.0	1.15
		32	81	24	301	329	1.0	69	11	113	5.8	3.2	1.23
		33	64	21	201	373	0.6	69	12	116	6.0	3.2	1.14
		34	67	27	292	286	1.0	73	18	126	5.7	3.0	1.11
		35	68	22	279	374	1.0	74	30	116	5.9	3.0	1.03
		Recovery											
		36	70	13	163	246	1.2	50	13	145	5.8	3.1	1.15
		37	72	26	177	420	0.9	82	23	120	5.8	2.8	0.93
		38	58	15	191	571	0.8	73	39	193	6.5	3.3	1.03
		39	72	19	310	334	1.1	52	13	129	5.6	3.0	1.15
		40	71	22	227	306	0.8	74	22	127	6.4	3.0	0.88
	50	41	68	16	270	339	0.4	89	22	101	6.0	3.1	1.07
		42	74	18	259	459	0.1	78	44	113	5.8	3.0	1.07
		43	76	22	341	131	2.2	82	22	123	5.7	3.0	1.11
		44	67	20	170	289	0.8	46	24	119	5.5	3.0	1.20
		45	89	19	315	450	1.1	48	12	112	6.0	3.2	1.14
	250	46	71	18	295	321	1.1	72	18	179	5.9	3.2	1.19
		47	72	19	300	369	1.1	63	57	120	6.2	3.2	1.07
		48	65	17	239	380	0.8	59	16	110	5.9	3.2	1.19
		49	65	22	157	296	0.9	65	16	120	5.9	3.1	1.11
		50	66	18	240	202	1.2	62	35	137	5.6	3.1	1.24
	1,000	51	61	14	219	202	0.7	78	27	122	5.4	3.0	1.25
		52	64	20	291	477	1.1	70	13	131	5.9	3.1	1.11
		53	77	35	275	310	1.0	62	28	138	6.1	3.1	1.03
		54	72	22	261	229	1.0	70	24	122	6.1	3.1	1.03
		55	65	23	217	275	1.1	66	22	108	5.9	3.3	1.27
		Recovery											
		56	78	28	222	403	1.1	52	11	118	5.8	3.0	1.07
		57	68	20	218	198	1.3	60	27	151	5.6	2.9	1.07
		58	77	23	257	395	1.1	58	10	135	6.4	3.2	1.00
		59	81	17	157	711	0.9	67	17	134	6.3	3.0	0.91
		60	65	20	221	257	1.0	47	9	127	5.9	3.1	1.11

Addendum 9-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Male	Vehicle control	1	14.4	0.24	0.08	9.8	8.8	142	4.0	103.0
		2	13.0	0.23	0.05	9.6	6.9	144	4.0	108.1
		3	16.9	0.22	0.09	9.5	8.3	142	4.1	106.3
		4	15.0	0.22	0.06	9.8	7.8	144	4.6	107.5
		5	13.9	0.19	0.06	10.0	8.2	143	4.0	105.4
		Recovery								
		6	13.5	0.26	0.04	9.4	6.6	140	4.1	104.1
		7	16.1	0.28	0.07	9.0	6.5	142	3.9	104.9
		8	17.6	0.27	0.07	9.7	7.7	141	4.4	104.4
		9	19.4	0.22	0.05	9.3	7.2	141	4.3	103.5
		10	15.0	0.24	0.05	9.5	7.3	141	4.6	105.4
	50	11	12.5	0.19	0.04	10.0	7.4	142	4.8	105.3
		12	13.5	0.23	0.05	9.6	8.0	142	5.1	107.6
		13	13.7	0.22	0.07	9.8	8.3	143	4.7	107.0
		14	15.3	0.20	0.08	9.8	8.2	143	4.1	106.3
		15	16.1	0.19	0.07	10.0	7.7	143	4.2	104.8
	250	16	19.5	0.23	0.05	9.8	8.4	142	4.5	106.4
		17	13.9	0.18	0.06	10.1	8.2	142	4.4	104.9
		18	19.4	0.19	0.10	10.2	8.3	142	4.4	104.7
		19	12.2	0.25	0.08	10.1	8.6	143	4.4	106.0
		20	11.4	0.18	0.07	9.9	7.9	142	4.5	107.2
	1,000	21	15.2	0.26	0.05	9.8	7.5	141	4.4	106.6
		22	20.0	0.31	0.06	9.6	8.3	139	4.3	101.2
		23	14.1	0.19	0.07	10.1	7.9	140	4.3	104.6
		24	12.0	0.23	0.07	10.0	8.4	142	4.1	107.1
		25	14.4	0.20	0.08	10.4	8.4	142	4.1	103.7
		Recovery								
		26	19.1	0.29	0.06	9.1	7.2	141	4.3	105.5
		27	13.3	0.22	0.08	9.5	6.8	142	4.1	104.4
		28	17.7	0.27	0.06	9.5	7.5	141	4.6	103.4
		29	15.8	0.24	0.06	9.5	7.1	142	4.0	105.0
		30	16.7	0.26	0.07	9.6	7.5	142	4.6	104.5

Addendum 9-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Blood chemical data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	BUN (mg/dL)	Creatinine (mg/dL)	T-Bil (mg/dL)	Ca (mg/dL)	IP (mg/dL)	Na (mEq/L)	K (mEq/L)	Cl (mEq/L)
Female	Vehicle control	31	17.4	0.26	0.07	9.7	7.7	142	4.1	107.6
		32	18.6	0.25	0.06	9.7	7.6	140	3.9	104.6
		33	15.2	0.29	0.06	9.4	6.5	140	3.9	106.6
		34	16.4	0.22	0.04	9.5	7.0	142	4.1	107.9
		35	12.9	0.20	0.05	10.2	7.9	141	4.7	106.9
		Recovery								
		36	14.9	0.28	0.07	9.3	5.4	142	3.9	108.5
		37	19.8	0.33	0.07	9.2	6.0	141	3.8	106.0
		38	17.3	0.30	0.06	9.7	5.8	138	3.5	102.4
		39	16.4	0.28	0.06	8.8	5.8	141	3.9	108.9
		40	17.6	0.33	0.07	9.5	6.4	140	3.7	105.4
	50	41	17.2	0.27	0.09	9.8	6.4	142	3.5	107.7
		42	14.6	0.24	0.06	9.9	7.0	142	4.2	108.2
		43	17.9	0.29	0.06	9.6	7.7	140	4.2	106.0
		44	16.9	0.28	0.05	9.5	6.8	140	3.7	108.3
		45	16.7	0.25	0.05	9.5	6.8	141	4.1	107.9
	250	46	19.6	0.29	0.05	9.7	6.7	140	3.8	106.6
		47	13.4	0.21	0.09	9.9	6.8	141	4.1	107.8
		48	18.5	0.27	0.06	9.8	7.6	140	4.1	106.5
		49	16.0	0.22	0.08	9.8	6.3	142	3.7	108.4
		50	14.0	0.24	0.05	10.4	7.7	139	4.9	105.8
	1,000	51	19.3	0.31	0.05	9.5	7.0	139	4.5	107.0
		52	19.4	0.29	0.05	9.9	6.1	137	4.1	105.5
		53	17.5	0.24	0.06	9.7	7.1	138	4.6	106.3
		54	14.3	0.24	0.08	9.8	6.7	140	3.9	106.2
		55	13.5	0.25	0.05	10.1	7.9	141	4.0	105.9
		Recovery								
		56	18.0	0.28	0.09	9.2	5.8	140	3.8	106.9
		57	17.6	0.22	0.06	9.0	6.5	141	3.8	107.3
		58	17.2	0.28	0.08	9.4	5.9	141	3.7	106.6
		59	18.2	0.28	0.07	9.5	6.4	142	4.0	105.9
		60	17.3	0.34	0.06	9.5	6.1	141	4.5	108.2

Addendum 10-1 Twenty-eight-day repeated-dose oral toxicity study in rats 811-0897
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Urine volume (mL)	Uosm (mOsm/L)
Male	Vehicle control	1	20	282
		2	24	260
		3	6	1256
		4	18	398
		5	16	545
		Recovery		
		6	7	1296
		7	10	1143
		8	7	1151
		9	5	2786
		10	15	648
	50	11	17	569
		12	25	207
		13	22	380
		14	9	832
		15	12	581
	250	16	7	1272
		17	18	462
		18	18	480
		19	17	351
		20	21	339
	1,000	21	19	412
		22	11	734
		23	20	417
		24	31	232
		25	20	450
		Recovery		
		26	6	1975
		27	11	789
		28	6	1600
		29	9	1489
		30	13	967

Addendum 10-2 Twenty-eight-day repeated-dose oral toxicity study in rats B11-0897
Urinalytic data of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Urine volume (mL)	Uosm (mOsm/L)
Female	Vehicle control	31	18	359
		32	9	938
		33	12	498
		34	4	1582
		35	12	713
		Recovery		
		36	3	1326
		37	7	1118
		38	5	1316
		39	6	1344
		40	10	768
	50	41	10	576
		42	9	686
		43	6	1161
		44	5	1299
		45	14	405
	250	46	5	878
		47	11	617
		48	9	765
		49	14	492
		50	8	805
	1,000	51	4	1671
		52	3	2252
		53	2	1745
		54	16	424
		55	15	485
		Recovery		
		56	9	744
		57	10	832
		58	10	784
		59	7	1022
		60	7	1091

Addendum 10-3 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Color	Turbidity	pH	Protein	Glucose	Occult blood
Male	Vehicle control	1	SY	NT	7.0	±	−	−
		2	SY	NT	6.5	±	−	−
		3	Y	NT	6.5	2+	−	−
		4	SY	NT	7.0	1+	−	−
		5	SY	NT	6.5	1+	−	−
		Recovery						
		6	SY	NT	7.0	1+	−	−
		7	SY	NT	6.5	±	−	−
		8	SY	NT	7.0	±	−	−
		9	Y	NT	6.5	1+	−	−
		10	SY	NT	7.0	±	−	−
	50	11	SY	NT	7.0	1+	−	−
		12	SY	NT	6.5	±	−	−
		13	SY	NT	6.5	±	−	−
		14	Y	NT	6.5	1+	−	−
		15	SY	NT	6.5	1+	−	−
	250	16	Y	NT	6.5	2+	−	−
		17	SY	NT	7.0	1+	−	−
		18	SY	NT	7.0	1+	−	−
		19	SY	NT	6.5	1+	−	−
		20	SY	NT	7.0	±	−	−
	1,000	21	SY	NT	6.5	±	−	−
		22	SY	NT	6.5	1+	−	−
		23	SY	NT	7.0	±	−	−
		24	SY	NT	6.5	±	−	−
		25	SY	NT	6.5	1+	−	−
		Recovery						
		26	Y	NT	6.0	1+	−	−
		27	Y	NT	7.0	±	−	−
		28	Y	NT	6.5	1+	−	−
		29	SY	NT	6.5	1+	−	−
		30	SY	NT	6.5	1+	−	−

SY, Slightly yellow.
Y, Yellow.
NT, No turbidity.

Addendum 10-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Color	Turbidity	pH	Protein	Glucose	Occult blood
Female	Vehicle control	31	SY	NT	6.5	−	−	−
		32	Y	NT	6.0	1+	−	−
		33	SY	NT	6.5	±	−	−
		34	Y	NT	6.0	2+	−	−
		35	SY	NT	6.5	1+	−	−
		Recovery						
		36	Y	NT	6.5	±	−	−
		37	SY	NT	6.0	±	−	−
		38	Y	NT	6.5	1+	−	−
		39	Y	NT	6.0	±	−	−
		40	SY	NT	6.0	±	−	−
	50	41	SY	NT	6.0	1+	−	−
		42	SY	NT	6.5	1+	−	−
		43	Y	NT	7.0	1+	−	−
		44	Y	NT	6.0	1+	−	−
		45	SY	NT	6.5	±	−	−
	250	46	Y	NT	7.0	1+	−	−
		47	SY	NT	6.5	±	−	−
		48	SY	NT	6.5	1+	−	−
		49	SY	NT	6.5	±	−	−
		50	SY	NT	6.0	1+	−	−
	1,000	51	Y	NT	6.0	1+	−	−
		52	Y	NT	6.0	2+	−	−
		53	Y	NT	6.5	2+	−	−
		54	SY	NT	6.5	±	−	−
		55	SY	NT	6.5	±	−	−
		Recovery						
		56	SY	NT	6.0	±	−	−
		57	SY	NT	6.5	±	−	−
		58	SY	NT	6.5	±	−	−
		59	SY	NT	6.5	±	−	−
		60	SY	NT	6.5	±	−	−

SY, Slightly yellow.
Y, Yellow.
NT, No turbidity.

Addendum 10-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals (Urinary sediment)

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Red blood cells[a]	White blood cells[a]	Epithelial cells[a]	Casts[b]	Crystals[c]
Male	Vehicle control	1	0	0	1	0	−
		2	0	0	0	0	−
		3	0	0	0	0	−
		4	0	0	2	0	+
		5	0	0	1	0	−
		Recovery					
		6 [d]	-	-	-	-	-
		7 [d]	-	-	-	-	-
		8 [d]	-	-	-	-	-
		9 [d]	-	-	-	-	-
		10 [d]	-	-	-	-	-
	50	11 [d]	-	-	-	-	-
		12 [d]	-	-	-	-	-
		13 [d]	-	-	-	-	-
		14 [d]	-	-	-	-	-
		15 [d]	-	-	-	-	-
	250	16 [d]	-	-	-	-	-
		17 [d]	-	-	-	-	-
		18 [d]	-	-	-	-	-
		19 [d]	-	-	-	-	-
		20 [d]	-	-	-	-	-
	1,000	21	0	0	1	0	−
		22	0	0	0	0	−
		23	0	0	1	0	−
		24	0	0	0	0	±
		25	0	1	1	0	−
		Recovery					
		26 [d]	-	-	-	-	-
		27 [d]	-	-	-	-	-
		28 [d]	-	-	-	-	-
		29 [d]	-	-	-	-	-
		30 [d]	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.
d) Not examined.

Addendum 10-6 Twenty-eight-day repeated-dose oral toxicity study in rats
Urinalytic data of individual animals (Urinary sediment)

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Red blood cells[a]	White blood cells[a]	Epithelial cells[a]	Casts[b]	Crystals[c]
Female	Vehicle control	31	0	0	0	0	−
		32	0	0	2	0	−
		33	0	0	0	0	−
		34	0	0	0	0	±
		35	0	0	2	0	−
		Recovery					
		36 [d]	-	-	-	-	-
		37 [d]	-	-	-	-	-
		38 [d]	-	-	-	-	-
		39 [d]	-	-	-	-	-
		40 [d]	-	-	-	-	-
	50	41 [d]	-	-	-	-	-
		42 [d]	-	-	-	-	-
		43 [d]	-	-	-	-	-
		44 [d]	-	-	-	-	-
		45 [d]	-	-	-	-	-
	250	46 [d]	-	-	-	-	-
		47 [d]	-	-	-	-	-
		48 [d]	-	-	-	-	-
		49 [d]	-	-	-	-	-
		50 [d]	-	-	-	-	-
	1,000	51	0	1	2	0	−
		52	0	0	0	0	−
		53	0	0	1	0	±
		54	0	0	0	0	−
		55	0	0	0	0	−
		Recovery					
		56 [d]	-	-	-	-	-
		57 [d]	-	-	-	-	-
		58 [d]	-	-	-	-	-
		59 [d]	-	-	-	-	-
		60 [d]	-	-	-	-	-

a) Number of cells/10 views (×400).
b) Number of casts/18×18 mm^2.
c) Incidence of crystals/18×18 mm^2.
d) Not examined.

Addendum 11-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

B11-0897

Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight (g)
Male	Vehicle control	1	8.98	1.05	2.31	2.85	0.63	-	2.06	0.61	556.6	40.6	312.9
		2	9.31	1.14	2.10	2.81	0.72	-	1.99	0.64	554.9	47.3	309.7
		3	8.76	1.08	1.97	2.89	0.68	-	2.01	0.47	534.4	46.8	286.5
		4	8.72	1.13	2.24	2.95	0.71	-	1.97	0.74	479.0	43.7	305.2
		5	8.61	1.02	2.05	3.26	0.72	-	1.87	0.71	575.6	42.6	287.0
		Recovery											
		6	10.78	1.12	2.62	3.04	1.01	-	2.04	0.62	528.4	64.4	385.8
		7	8.33	1.04	2.15	3.11	0.96	-	1.88	0.54	586.7	47.2	334.8
		8	9.84	1.18	2.53	3.04	0.94	-	1.98	0.62	360.2	45.3	372.9
		9	11.48	1.32	2.87	3.27	1.04	-	2.15	0.91	726.3	50.7	394.1
		10	9.22	1.11	2.42	3.07	0.93	-	1.96	0.59	385.2	47.9	351.3
	50	11	10.93	1.23	2.81	3.30	0.87	-	2.00	0.72	574.4	49.4	343.1
		12	8.34	1.11	2.12	3.12	0.70	-	1.79	0.69	398.4	49.5	282.6
		13	9.58	1.07	2.24	2.84	0.69	-	1.94	0.64	543.2	46.0	311.1
		14	9.47	1.14	2.58	3.14	0.70	-	2.01	0.69	435.1	40.2	312.5
		15	8.86	1.05	2.32	2.91	0.69	-	2.02	0.72	523.7	43.4	298.8
	250	16	9.85	1.23	2.65	3.08	0.63	-	1.95	0.59	639.2	51.1	338.4
		17	9.50	1.28	2.37	2.78	0.65	-	2.02	0.62	615.5	57.7	318.8
		18	11.01	1.16	2.21	3.13	0.80	-	1.92	0.77	710.7	47.6	331.8
		19	9.25	1.05	2.16	3.08	0.69	-	1.86	0.62	667.6	47.4	314.4
		20	8.66	1.21	2.27	2.94	0.70	-	2.04	0.61	789.3	43.2	311.6
	1,000	21	9.03	1.20	2.04	3.26	0.72	-	2.04	0.62	558.0	45.4	298.0
		22	9.60	1.04	1.98	2.87	0.63	-	2.01	0.64	547.8	61.8	316.8
		23	11.20	1.24	2.77	3.20	0.82	-	2.29	0.76	863.1	49.1	347.0
		24	8.85	1.15	2.27	2.91	0.72	-	1.90	0.60	516.9	72.4	301.5
		25	12.18	1.37	2.70	2.95	0.77	-	2.00	0.75	704.3	64.1	368.8
		Recovery											
		26	8.04	1.09	2.03	2.76	0.77	-	1.93	0.53	393.6	38.7	334.0
		27	9.58	1.25	2.70	3.31	0.94	-	2.05	0.65	356.7	56.8	364.1
		28	10.04	1.14	2.48	3.35	0.91	-	1.96	0.56	500.6	57.4	372.2
		29	11.05	1.22	2.73	3.22	1.01	-	2.20	0.80	553.1	60.0	383.1
		30	11.73	1.33	2.23	2.81	0.89	-	2.08	0.64	538.7	57.9	423.2

Addendum 11-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Absolute organ weights of individual animals

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Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g)	Heart (g)	Kidney (g)	Testis (g)	Epididymis (g)	Ovary (mg)	Brain (g)	Spleen (g)	Thymus (mg)	Adrenal (mg)	Body weight (g)
Female	Vehicle control	31	6.12	0.83	1.54	-	-	79.6	1.89	0.45	492.1	59.0	209.5
		32	6.50	0.76	1.63	-	-	102.2	1.89	0.51	590.5	73.2	217.9
		33	5.83	0.77	1.64	-	-	80.8	1.88	0.37	438.2	67.0	193.8
		34	6.40	0.82	1.57	-	-	77.5	1.84	0.59	398.6	71.5	201.6
		35	6.68	0.81	1.91	-	-	95.7	1.94	0.55	485.5	79.7	225.7
		Recovery											
		36	5.52	0.67	1.46	-	-	73.7	1.84	0.31	326.1	68.4	198.0
		37	6.10	0.73	1.63	-	-	79.7	1.96	0.43	391.4	65.2	239.0
		38	6.92	0.88	1.71	-	-	81.9	1.96	0.43	492.0	76.7	229.8
		39	5.01	0.73	1.56	-	-	84.7	2.02	0.43	304.3	58.5	191.8
		40	6.46	0.78	1.57	-	-	88.4	1.86	0.41	442.0	61.5	248.3
	50	41	6.18	0.75	1.44	-	-	78.9	1.81	0.44	590.2	57.4	199.6
		42	5.63	0.78	1.60	-	-	74.7	1.94	0.42	545.3	70.6	195.6
		43	6.30	0.79	1.57	-	-	84.9	1.82	0.49	380.4	74.0	200.3
		44	6.02	0.71	1.51	-	-	75.4	1.77	0.45	386.1	93.5	198.4
		45	5.30	0.73	1.56	-	-	76.3	1.88	0.36	320.6	75.2	184.8
	250	46	6.02	0.76	1.33	-	-	84.4	1.81	0.39	489.3	60.9	187.3
		47	5.87	0.78	1.55	-	-	76.2	1.81	0.38	355.0	66.7	200.5
		48	6.01	0.88	1.61	-	-	79.8	1.83	0.43	541.0	56.4	212.0
		49	6.29	0.82	1.62	-	-	80.1	1.95	0.51	479.7	69.3	215.2
		50	6.85	0.95	1.73	-	-	85.9	1.91	0.45	670.7	77.9	221.3
	1,000	51	5.65	0.89	1.55	-	-	86.5	1.86	0.46	597.1	60.6	195.5
		52	6.08	0.78	1.69	-	-	79.1	1.76	0.36	500.4	66.5	208.2
		53	6.11	0.80	1.53	-	-	72.0	1.83	0.56	447.5	64.3	192.1
		54	6.33	0.74	1.62	-	-	99.0	1.93	0.48	521.7	73.1	210.5
		55	6.66	0.90	1.65	-	-	82.4	1.91	0.47	515.0	70.8	220.3
		Recovery											
		56	5.98	0.77	1.67	-	-	102.4	1.86	0.39	405.0	66.2	227.6
		57	5.27	0.69	1.47	-	-	58.0	1.84	0.43	386.7	51.8	212.0
		58	6.13	0.76	1.56	-	-	84.2	1.90	0.36	362.6	64.5	233.4
		59	6.64	0.79	1.81	-	-	72.7	2.13	0.48	493.7	65.0	233.7
		60	6.38	0.76	1.51	-	-	74.7	1.90	0.49	375.9	71.8	219.0

Addendum 12-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Relative organ weights of individual animals

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Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight (g)
Male	Vehicle control	1	2.87	0.34	0.74	0.91	0.20	-	0.66	0.19	177.9	13.0	312.9
		2	3.01	0.37	0.68	0.91	0.23	-	0.64	0.21	179.2	15.3	309.7
		3	3.06	0.38	0.69	1.01	0.24	-	0.70	0.16	186.5	16.3	286.5
		4	2.86	0.37	0.73	0.97	0.23	-	0.65	0.24	156.9	14.3	305.2
		5	3.00	0.36	0.71	1.14	0.25	-	0.65	0.25	200.6	14.8	287.0
		Recovery											
		6	2.79	0.29	0.68	0.79	0.26	-	0.53	0.16	137.0	16.7	385.8
		7	2.49	0.31	0.64	0.93	0.29	-	0.56	0.16	175.2	14.1	334.8
		8	2.64	0.32	0.68	0.82	0.25	-	0.53	0.17	96.6	12.1	372.9
		9	2.91	0.33	0.73	0.83	0.26	-	0.55	0.23	184.3	12.9	394.1
		10	2.62	0.32	0.69	0.87	0.26	-	0.56	0.17	109.6	13.6	351.3
	50	11	3.19	0.36	0.82	0.96	0.25	-	0.58	0.21	167.4	14.4	343.1
		12	2.95	0.39	0.75	1.10	0.25	-	0.63	0.24	141.0	17.5	282.6
		13	3.08	0.34	0.72	0.91	0.22	-	0.62	0.21	174.6	14.8	311.1
		14	3.03	0.36	0.83	1.00	0.22	-	0.64	0.22	139.2	12.9	312.5
		15	2.97	0.35	0.78	0.97	0.23	-	0.68	0.24	175.3	14.5	298.8
	250	16	2.91	0.36	0.78	0.91	0.19	-	0.58	0.17	188.9	15.1	338.4
		17	2.98	0.40	0.74	0.87	0.20	-	0.63	0.19	193.1	18.1	318.8
		18	3.32	0.35	0.67	0.94	0.24	-	0.58	0.23	214.2	14.3	331.8
		19	2.94	0.33	0.69	0.98	0.22	-	0.59	0.20	212.3	15.1	314.4
		20	2.78	0.39	0.73	0.94	0.22	-	0.65	0.20	253.3	13.9	311.6
	1,000	21	3.03	0.40	0.68	1.09	0.24	-	0.68	0.21	187.2	15.2	298.0
		22	3.03	0.33	0.63	0.91	0.20	-	0.63	0.20	172.9	19.5	316.8
		23	3.23	0.36	0.80	0.92	0.24	-	0.66	0.22	248.7	14.1	347.0
		24	2.94	0.38	0.75	0.97	0.24	-	0.63	0.20	171.4	24.0	301.5
		25	3.30	0.37	0.73	0.80	0.21	-	0.54	0.20	191.0	17.4	368.8
		Recovery											
		26	2.41	0.33	0.61	0.83	0.23	-	0.58	0.16	117.8	11.6	334.0
		27	2.63	0.34	0.74	0.91	0.26	-	0.56	0.18	98.0	15.6	364.1
		28	2.70	0.31	0.67	0.90	0.24	-	0.53	0.15	134.5	15.4	372.2
		29	2.88	0.32	0.71	0.84	0.26	-	0.57	0.21	144.4	15.7	383.1
		30	2.77	0.31	0.53	0.66	0.21	-	0.49	0.15	127.3	13.7	423.2

Addendum 12-2 Twenty-eight-day repeated-dose oral toxicity study in rats
Relative organ weights of individual animals

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Sex	Exp.group (mg/kg/day)	Animal No.	Liver (g/100g)	Heart (g/100g)	Kidney (g/100g)	Testis (g/100g)	Epididymis (g/100g)	Ovary (mg/100g)	Brain (g/100g)	Spleen (g/100g)	Thymus (mg/100g)	Adrenal (mg/100g)	Body weight (g)
Female	Vehicle control	31	2.92	0.40	0.74	-	-	38.0	0.90	0.21	234.9	28.2	209.5
		32	2.98	0.35	0.75	-	-	46.9	0.87	0.23	271.0	33.6	217.9
		33	3.01	0.40	0.85	-	-	41.7	0.97	0.19	226.1	34.6	193.8
		34	3.17	0.41	0.78	-	-	38.4	0.91	0.29	197.7	35.5	201.6
		35	2.96	0.36	0.85	-	-	42.4	0.86	0.24	215.1	35.3	225.7
		Recovery											
		36	2.79	0.34	0.74	-	-	37.2	0.93	0.16	164.7	34.5	198.0
		37	2.55	0.31	0.68	-	-	33.3	0.82	0.18	163.8	27.3	239.0
		38	3.01	0.38	0.74	-	-	35.6	0.85	0.19	214.1	33.4	229.8
		39	2.61	0.38	0.81	-	-	44.2	1.05	0.22	158.7	30.5	191.8
		40	2.60	0.31	0.63	-	-	35.6	0.75	0.17	178.0	24.8	248.3
	50	41	3.10	0.38	0.72	-	-	39.5	0.91	0.22	295.7	28.8	199.6
		42	2.88	0.40	0.82	-	-	38.2	0.99	0.21	278.8	36.1	195.6
		43	3.15	0.39	0.78	-	-	42.4	0.91	0.24	189.9	36.9	200.3
		44	3.03	0.36	0.76	-	-	38.0	0.89	0.23	194.6	47.1	198.4
		45	2.87	0.40	0.84	-	-	41.3	1.02	0.19	173.5	40.7	184.8
	250	46	3.21	0.41	0.71	-	-	45.1	0.97	0.21	261.2	32.5	187.3
		47	2.93	0.39	0.77	-	-	38.0	0.90	0.19	177.1	33.3	200.5
		48	2.83	0.42	0.76	-	-	37.6	0.86	0.20	255.2	26.6	212.0
		49	2.92	0.38	0.75	-	-	37.2	0.91	0.24	222.9	32.2	215.2
		50	3.10	0.43	0.78	-	-	38.8	0.86	0.20	303.1	35.2	221.3
	1,000	51	2.89	0.46	0.79	-	-	44.2	0.95	0.24	305.4	31.0	195.5
		52	2.92	0.37	0.81	-	-	38.0	0.85	0.17	240.3	31.9	208.2
		53	3.18	0.42	0.80	-	-	37.5	0.95	0.29	233.0	33.5	192.1
		54	3.01	0.35	0.77	-	-	47.0	0.92	0.23	247.8	34.7	210.5
		55	3.02	0.41	0.75	-	-	37.4	0.87	0.21	233.8	32.1	220.3
		Recovery											
		56	2.63	0.34	0.73	-	-	45.0	0.82	0.17	177.9	29.1	227.6
		57	2.49	0.33	0.69	-	-	27.4	0.87	0.20	182.4	24.4	212.0
		58	2.63	0.33	0.67	-	-	36.1	0.81	0.15	155.4	27.6	233.4
		59	2.84	0.34	0.77	-	-	31.1	0.91	0.21	211.3	27.8	233.7
		60	2.91	0.35	0.69	-	-	34.1	0.87	0.22	171.6	32.8	219.0

Addendum 13-1 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	Vehicle control	1	ta	No abnormalities detected	No abnormalities detected
		2	ta	No abnormalities detected	No abnormalities detected
		3	ta	No abnormalities detected	No abnormalities detected
		4	ta	No abnormalities detected	No abnormalities detected
		5	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: trachea, lungs, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

Addendum 13-2 *Twenty-eight-day repeated-dose oral toxicity study in rats*
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	Vehicle control (*Recovery*)	6	ta	No abnormalities detected	Not examined
		7	ta	No abnormalities detected	Not examined
		8	ta	No abnormalities detected	Not examined
		9	ta	Glandular stomach Elevated region of mucosa (ϕ 2 mm)	Glandular stomach Squamous epithelial cyst +
		10	ta	Spleen Whitish region on capsule (multiple, spotty- ϕ 3 mm)	Spleen Capsulitis +

a) Organs/tissues examined as follows: macroscopic lesion.
ta, terminal autopsy.
+, slight.

Addendum 13-3 Twenty-eight-day repeated-dose oral toxicity study in rats

Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings
Male	50	11	ta	No abnormalities detected	Not examined
		12	ta	No abnormalities detected	Not examined
		13	ta	No abnormalities detected	Not examined
		14	ta	No abnormalities detected	Not examined
		15	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

Addendum 13-4 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	250	16	ta	No abnormalities detected	Not examined
		17	ta	No abnormalities detected	Not examined
		18	ta	No abnormalities detected	Not examined
		19	ta	Skin	Skin
				Loss of hair (right forelimb)	No abnormalities detected
		20	ta	No abnormalities detected	Not examined

a) Organs/tissues examined as follows: macroscopic lesion.
ta, terminal autopsy.

Addendum 13-5 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Male	1,000	21	ta	No abnormalities detected	No abnormalities detected
		22	ta	No abnormalities detected	No abnormalities detected
		23	ta	Kidney Pelvic dilatation (left)	Kidney Pelvic dilatation, unilateral +
		24	ta	No abnormalities detected	No abnormalities detected
		25	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: trachea, lungs, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, testes, epididymides, prostate, seminal vesicle, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight.

Addendum 13-6 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings
Male	1,000 (Recovery)	26	ta	No abnormalities detected	Not examined
		27	ta	No abnormalities detected	Not examined
		28	ta	No abnormalities detected	Not examined
		29	ta	No abnormalities detected	Not examined
		30	ta	No abnormalities detected	Not examined

ta, terminal autopsy.

Addendum 13-7 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	Vehicle control	31	ta	No abnormalities detected	No abnormalities detected
		32	ta	No abnormalities detected	No abnormalities detected
		33	ta	No abnormalities detected	Kidney Subcapsular cyst formation + Pituitary gland Rathke's pouch remnant +
		34	ta	No abnormalities detected	Liver Microgranuloma + Kidney Mineralization in cortico-medullary junction +
		35	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: trachea, lungs, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, ovaries, uterus, vagina, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight.

Addendum 13-8 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	Vehicle control (Recovery)	36	ta	No abnormalities detected	No abnormalities detected
		37	ta	No abnormalities detected	No abnormalities detected
		38	ta	No abnormalities detected	No abnormalities detected
		39	ta	No abnormalities detected	No abnormalities detected
		40	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: spleen.
ta, terminal autopsy.

Addendum 13-9 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	*Macroscopic findings*	*Histopathological findings*[a)]
Female	50	41	ta	No abnormalities detected	No abnormalities detected
		42	ta	No abnormalities detected	No abnormalities detected
		43	ta	No abnormalities detected	No abnormalities detected
		44	ta	No abnormalities detected	No abnormalities detected
		45	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: spleen.
ta, terminal autopsy.

Addendum 13-10 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	250	46	ta	No abnormalities detected	No abnormalities detected
		47	ta	No abnormalities detected	No abnormalities detected
		48	ta	No abnormalities detected	No abnormalities detected
		49	ta	No abnormalities detected	No abnormalities detected
		50	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: spleen.
ta, terminal autopsy.

Addendum 13-11 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	1,000	51	ta	No abnormalities detected	Liver Microgranuloma + Thyroid Ectopic thymic tissue +
		52	ta	Thyroid Decreased in size of left lobe	Thyroid Aplasia of left lobe
		53	ta	Spleen Nodule (ϕ 10 mm)	Spleen Hyperplasia of lymphoid cells ++
		54	ta	No abnormalities detected	No abnormalities detected
		55	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: trachea, lungs, forestomach, glandular stomach, duodenum, jejunum, ileum, cecum, colon, rectum, liver, heart, kidneys, urinary bladder, ovaries, uterus, vagina, cerebrum, cerebellum, pons, spinal cord, sciatic nerve, bone marrow, axillar lymph node, mesenteric lymph node, spleen, thymus, pituitary gland, thyroid, parathyroid, adrenals and eye ball.

ta, terminal autopsy.

+, slight; ++, moderate.

Addendum 13-12 Twenty-eight-day repeated-dose oral toxicity study in rats
Pathological findings of individual animals

Sex	Exp.group (mg/kg/day)	Animal No.	Fate	Macroscopic findings	Histopathological findings[a)]
Female	1,000 (Recovery)	56	ta	No abnormalities detected	No abnormalities detected
		57	ta	No abnormalities detected	No abnormalities detected
		58	ta	No abnormalities detected	No abnormalities detected
		59	ta	No abnormalities detected	No abnormalities detected
		60	ta	No abnormalities detected	No abnormalities detected

a) Organs/tissues examined as follows: spleen.
ta, terminal autopsy.

PHYSICOCHEMICAL REPORT

CERI

Receipt No. 827-08-D-3365

STUDY CODE: X18-0897

FINAL REPORT

HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF FORMULATION

January 2009

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

STATEMENT

TITLE OF STADY

Homogeneity, Stability and Concentration Analyses of Formulation (Study Code: X18-0897)

I, the undersigned, hereby declare that this report provides a correct English translation of the final report (Study Code: X18-0897, issued on January 8, 2009).

Yuji Kusune

Yuji Kusune, M.S.
Hita Laboratory
Chemicals Evaluation and Research Institute, Japan

July 2, 2009

Date

GLP STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Title: Homogeneity, Stability and Concentration Analyses of Formulation

Study Code: X18-0897

I, the undersigned, hereby declare that this study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)).

I also confirmed that this report accurately reflected the raw data and the test data were valid.

Study Director: Signed in original January 8, 2009

Yuji Kusune, M.S.

QUALITY ASSURANCE STATEMENT

Hita Laboratory

Chemicals Evaluation and Research Institute, Japan

Title: Homogeneity, Stability and Concentration Analyses of Formulation

Study Code: X18-0897

This study was inspected by Quality Assurance Unit of Hita Laboratory, Chemicals Evaluation and Research Institute, Japan. The dates inspected and the dates reported these results to the study director and management are as follows

Phase	Date of Inspection	Date Reported to Study Director and Management
Protocol	August 21, 2008	August 21, 2008
Homogeneity and Stability Analyses of Test Substance Formulation	August 22, 2008	August 22, 2008
Confirmation of the Answer from Study Director (Protocol)	August 26, 2008	August 27, 2008
Amendment to Protocol	September 2, 2008	September 2, 2008
Concentration Analysis of Test Substance Formulation	September 5, 2008	September 5, 2008
Raw Data and Draft Final Report	January 6, 2009	January 6, 2009
Reinspection of Raw Data and Draft Final Report	January 7, 2009	January 7, 2009
Final Report	January 8, 2009	January 8, 2009

I, the undersigned, hereby declare that this report provides an accurate description of the methods and procedures used in this study, and that the reported results accurately reflect obtained raw data.

Head, Quality Assurance Unit: Signed in original January 8, 2009

Ryuichiro Mizuguchi, B.S.

ALL CIRCLED INFORMATION
IS CONFIDENTIAL

TABLE OF CONTENTS

Study Code: X18-0897
Test Substance Code: HR7578
Sponsor Code: I-0010

TITLE

Homogeneity, Stability and Concentration Analyses of Formulation

SPONSOR

TESTING FACILITY

Hita Laboratory
Chemicals Evaluation and Research Institute, Japan
822, 3-chome, Ishii-machi, Hita, Oita 877-0061, Japan

PURPOSE OF STUDY

The purpose of this study is to determine homogeneity, stability and concentration of the test substance in formulation in "Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of LTO in Rats" (Study Code: B11-0897).

GLP COMPLIANCE

This study was conducted in compliance with "Concerning Standard of the Testing Facilities Conducting the Test Relating to the New Chemical Substances" on Japanese GLP (Notification No. 1121003 of the Pharmaceutical and Food Safety Bureau, MHLW, No. 3 (November 17, 2003) of the Manufacturing Industries Bureau, METI & No. 031121004 of the Environmental Health Department, MOE (November 21, 2003)).

PERIOD OF STUDY

Commencement of Study:	August 19, 2008
Initiation of Examination (Initiation of Analysis):	August 22, 2008
Termination of Examination (Termination of Analysis):	September 8, 2008
Completion of Study:	January 8, 2009

STORAGE AND RETENTION PERIOD OF DATA

The raw data, protocol, amendment to protocol, study contract documents, test substance information, final report and other record documents will be retained in the archive of the Hita Laboratory of our organization for the same period of B11-0897 paper data. After termination of the retention period, any measures taken will be done so with the approval of the sponsor.

RETENTION OF ORIGINAL DOCUMENTS

An original protocol, an original amendment to protocol and an original final report will be retained at Hita Laboratory. The copies of their original that the study director will be recognized to be accurate copy will be sent to the sponsor.

STUDY DIRECTOR AND PERSONS CONCERNED WITH THE STUDY AND THE OPERATION

Study director: Yuji Kusune, M.S.

Study staff: Yuji Kusune, M.S.
(Analysis of the test substance)

Masaya Matsumoto, B.S.
(Preparation of the test substance formulation)

APPROVAL BY AUTHOR

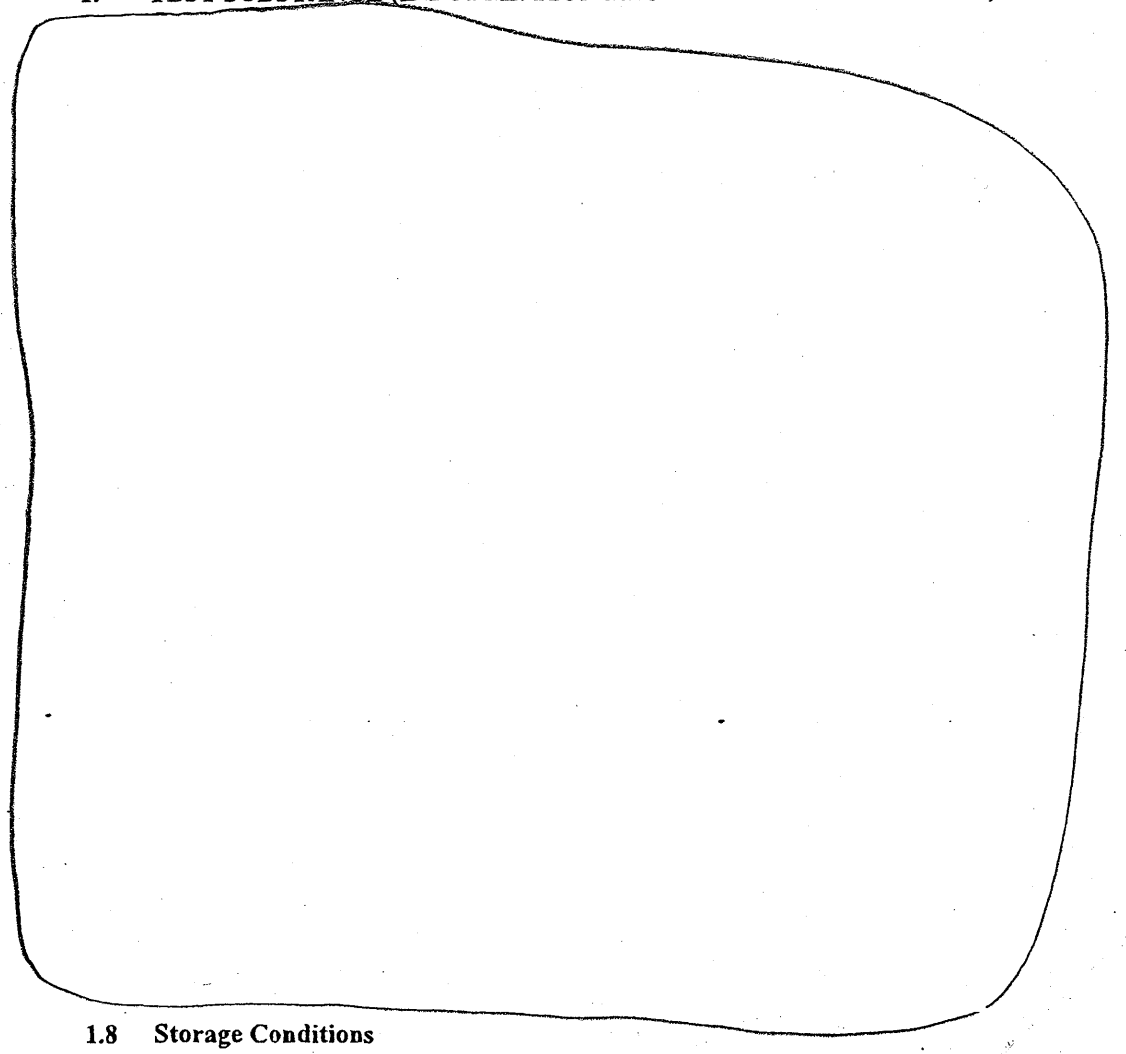
Study director: Signed in original January 8, 2009
Yuji Kusune, M.S.
Analytical Chemistry Section
Hita Laboratory

SUMMARY

The test substance [redacted] in 10.0 and 0.5 w/v% formulations was stable for 11 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 10.0, 2.5 and 0.5 w/v% dose formulations for subject study (Study Code: B11-0897) was acceptable level.

MATERIALS

1. TEST SUBSTANCE (INFORMATION PROVIDED BY THE SPONSOR)



1.8 Storage Conditions

Stored at room temperature (cabinet No. 7 in test substance storage room, tolerance temperature: 10-30°C). Actual temperature between received of test substance to termination of examination was 20.6-22.8°C. It satisfied tolerance.

1.9 Handling Precaution

Glove, mask, cap, protective glasses and lab coat were worn.

METHODS

1. SUBJECT STUDY

Twenty-Eight-Day Repeated-Dose Oral Toxicity Study of in Rats (Study Code:

B11-0897)

2. HOMOGENEITY, STABILITY AND CONCENTRATION ANALYSES OF THE TEST SUBSTANCE FORMULATION

In the homogeneity analysis, the samples were taken (n=1) from the upper, middle and lower layers of formulations immediately after preparation, respectively. These samples were dried in weighing bottle, residues were weighed (n=1) (gravimetric analysis), and concentration of test substance was determined. In addition, because the results at first time preparation were not satisfied criteria for judgment (a rate to the nominal concentration for the actual concentration: 103-111% (10.0 w/v% formulation), 107-114% (0.5 w/v% formulation)), they were rejected. Formulations were prepared again, and the homogeneity analysis was carried out using formulations of second time preparation. At sampling from formulation, Multipette plus 4981 was used at first time preparation, and measuring pipette was used at second time preparation.

In the stability analysis, the formulations were stored at cold and dark place for 11 days, and the sample was taken (n=1) from the middle layer of the formulations at point of measurement (after 7 days and 12 days after preparation). These samples were dried in weighing bottle, residues were weighed (n=1), and concentration of test substance was determined.

In the concentration analysis, the samples were taken (n=1) from the middle layer of dose formulations immediately after preparation for subject study. These samples were dried in weighing bottle, residues were weighed (n=1), and concentration of test substance was determined.

2.1 The Test Substance Formulation

1) Homogeneity and Stability Analyses

(1) Concentration

10.0 and 0.5 w/v%

(2) Preparation Method

The test substance was accurately weighed and mixed with purified water to prepare 10.0 w/v% formulation. 0.5 w/v% formulation was diluted from 10.0 w/v% formulation with purified water.

Preparation	Test substance sampling weight (g)	10.0 w/v% formulation final volume (mL)	10.0 w/v% formulation sampling volume (mL)	0.5 w/v% formulation final volume (mL)
First time (reject)	5.00	50	10	200
Second time	10.00	100	15	300

Vehicle: purified water (Lot No. 080613A, Takasugi Pharmaceutical Co., Ltd.)

2) Concentration Analysis

The 10.0, 2.5 and 0.5 w/v% dose formulations at first preparation for subject study were used.

2.2 Outline of Analytical Method

The analytical method was decided, according to results of validation of the analytical method on non-GLP at the test facility. In addition, theoretical value of sampling weight from formulations was 0.1 g (10.0 w/v% formulation: 1 mL, 2.5 w/v% formulation: 4 mL, 0.5 w/v% formulation: 20 mL).

1) Validation of the Analytical Method

(1) Specificity

The weighing bottle was dried for 31 minutes under reduced pressure in desiccator (desiccant: silica gel) and weighed (weight before adding of blank). After adding of 20 mL of purified water (solvent and vehicle blank) to weighing bottle (n=3), there were evaporated for 60 minutes by hot plate (NA-1, AS ONE corporation, set temperature 200°C). There were dried for 78 minutes under reduced pressure in desiccator and weighed (weight after adding of blank).

The weights of residue in solvent and vehicle blank were 0.0000, 0.0000 and 0.0002 g. Because these results were less than 0.2% of theoretical value, it was confirmed that there were no effect to result.

(2) Accuracy (Recovery Rate) and Repeatability

The weighing bottle was dried for 31 minutes under reduced pressure in desiccator and weighed (weight before adding of test substance). Approximately 0.1 g of the test substance and 20 mL of purified water was added to weighing bottle (n=6), there were evaporated for 60 minutes by hot plate. There were dried for 78 minutes under reduced pressure in desiccator and weighed (weight after adding of test substance).

Accuracy (recovery rate) was 101,100,101,101,101 and 101% and repeatability was 0.4%. It was confirmed that the result of accuracy and repeatability satisfied criteria for judgment (accuracy: within 100±10%, repeatability: less than 5%).

2) Pre-Treatment

Formulations were mixed well using a magnetic stirrer. In addition, the weighing bottle was used that dried for 30 minutes or more under reduced pressure in desiccator and weighed (weight before adding of formulation).

(1) 10.0 w/v% Formulation (Homogeneity, Stability and Concentration Analyses)

Accurate 1 mL of formulation was sampling to weighing bottle. After adding 19 mL of purified water, it was evaporated for 60 minutes by hot plate. It was dried for 80 minutes or more under reduced pressure in desiccator and weighed (weight after adding of formulation).

(2) 2.5 w/v% Formulation (Concentration Analysis)

Accurate 4 mL of formulation was sampling to weighing bottle. After adding 16 mL of purified water, it was evaporated for 60 minutes by hot plate. It was dried for 80 minutes or more under reduced pressure in desiccator and weighed (weight after adding of formulation).

(3) 0.5 w/v% Formulation (Homogeneity, Stability and Concentration Analyses)

Accurate 20 mL of formulation was sampling to weighing bottle. It was evaporated for 60 minutes by hot plate. It was dried for 80 minutes or more under reduced pressure in desiccator and weighed (weight after adding of formulation).

3) Instrument for Weighing

Electron analysis balance: LA230S (Sartorius K.K.)

2.3 Data Processing

1) Detection Value

The weight (g) measured with electron analysis balance was used the detection value.

2) Calculation of the Test Substance Concentration in Formulation

Concentration of test substance in each sample (C: w/v%) was calculated with the equation shown below and rounded off to three significant figures.

$$W_2 = W_1 - W_0$$

$$C = \frac{W_2}{V_0} \times 100$$

W_0: weight before adding of formulation (g)

W_1: weight after adding of formulation (g)

W_2: weight of residue (g)

V_0: volume of formulation (mL)

2.4 Criteria for Judgment

1) Homogeneity Analysis

The test substance was judged as homogeneous dispersion in vehicle if a coefficient of variation (CV) was within 5%. The CV was calculated using the following equation:

$$CV(\%) = \frac{\text{Standard deviation for concentration of test substance in each layer}}{\text{Mean concentration of test substance in each layer}} \times 100$$

2) Stability Analysis

The test substance was judged as stable state in vehicle if a rate to the nominal concentration for the actual concentration (R.N.) and a rate to the mean concentration immediately after preparation for the actual concentration (R.P.) were within the range of 100±10%. The R.N. and R.P. were calculated using the following equation:

$$\text{R.N.}(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

$$\text{R.P.}(\%) = \frac{\text{Actual concentration}}{\text{Mean concentration immediately after preparation}} \times 100$$

3) Concentration Analysis

It was confirmed that R.N. was within the range of 100±10%. The R.N. was calculated using the following equation:

$$\text{R.N.}(\%) = \frac{\text{Actual concentration}}{\text{Nominal concentration}} \times 100$$

ENVIRONMENTAL FACTORS THAT MIGHT HAVE AFFECTED RELIABILITY OF STUDY RESULTS

There were no factors that might have affected the reliability of the study data.

RESULTS AND DISCUSSION

1. RESULTS

1.1 Homogeneity, Stability and Concentration Analyses of the Test Substance Formulation

1) Homogeneity and Stability Analyses

The results of homogeneity and stability analyses of the test substance formulation are shown in Table 1.

(1) Homogeneity Analysis

CV of 10.0 and 0.5 w/v% formulations were 1.0 and 0.3%, respectively. The results satisfied criteria for judgment.

(2) Stability Analysis

a) 10.0 w/v% Formulation

At immediately after preparation, R.N. were 101 to 103%.

At 7 days after preparation, R.N. was 100%, and R.P. was 98.0%.

At 12 days after preparation, R.N. was 101%, and R.P. was 99.0%.

All the results of R.N. and R.P. satisfied criteria for judgment.

b) 0.5 w/v% Formulation

At immediately after preparation, R.N. were 92.6 to 93.2%.

At 7 days after preparation, R.N. was 910%, and R.P. was 98.1%.

At 12 days after preparation, R.N. was 92.0%, and R.P. was 99.1%.

All the results of R.N. and R.P. satisfied criteria for judgment.

2) Concentration Analysis

The results of concentration analysis of the test substance formulation are shown in Table 2.

R.N. of 10.0, 2.5 and 0.5 w/v% dose formulations were 96.0 to 97.9%. All the results satisfied criteria for judgment.

2. DISCUSSION

The test substance in 10.0 and 0.5 w/v% formulations was stable for 11 days after preparation at cold and dark place and showed good homogeneity. The concentration of test substance in 10.0, 2.5 and 0.5 w/v% dose formulations for subject study was acceptable level.

Table 1 Homogeneity and stability analyses of the test substance formulation

Nominal conc. (w/v%)	Time point of measurement	Layer of measurement	Actual conc. (w/v%)	R.N. (%)	Mean conc. (w/v%)	R.P. (%)	CV (%)
10.0	Immediately after preparation	Upper	10.3	103	10.2	-	1.0
		Middle	10.1	101			
		Lower	10.2	102			
	7 days after preparation	Middle	10.0	100	-	98.0	-
	12 days after preparation	Middle	10.1	101	-	99.0	-
0.5	Immediately after preparation	Upper	0.464	92.8	0.464	-	0.3
		Middle	0.466	93.2			
		Lower	0.463	92.6			
	7 days after preparation	Middle	0.455	91.0	-	98.1	-
	12 days after preparation	Middle	0.460	92.0	-	99.1	-

R.N.: Rate to the nominal concentration

R.P.: Rate to the concentration measured immediately after preparation

CV: Coefficient of variation

Table 2 Concentration analysis of the dose formulation

Date of analysis	Nominal conc. (w/v%)	Actual conc. (w/v%)	R.N. (%)
September 5, 2008	10.0	9.79	97.9
	2.5	2.40	96.0
	0.5	0.481	96.2

R.N.: Rate to the nominal concentration

X-RAY DIFFRACTION RESULTS

B11-0897

X-RAY DIFFRACTION RESULTS

Test substance:

Test facility: Tokyo Laboratory
Chemicals Evaluation and Research Institute, Japan

Dates : August 26, 2008 (Before dosing period)
December 11, 2008 (After dosing period)

Analytical methods

Instrument:	X-ray diffraction, X' Pert PRO MPD (PANalytical)
Target:	Cu
Applied voltage:	45 kV
Applied current:	40 mA
Detector:	X' Celerator
Scan range (2θ):	10-70°
Divergent slit:	(1/2)°
Soller slit:	1°
Scan step time:	200 S

Results

X-ray diffraction spectrum of test substance provided by the sponsor (Fig. 1) were identical with those measured before dosing period (Fig. 2).

There were no differences in the X-ray diffraction spectrum between before and after dosing period (Fig. 1 and 2).

It was judged that the test substance was stable during the dosing period.