

Sunshine Act Meetings

Federal Register

Vol. 59, No. 158

Wednesday, August 17, 1994

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 11 a.m., Friday
September 2, 1994.

PLACE: 2033 K St., NW., Washington, DC, 8th Floor Hearing Room.

STATUS: Closed.

MATTERS TO BE CONSIDERED: Surveillance Matters.

CONTACT PERSON FOR MORE INFORMATION:

Jean A. Webb, 254-6314.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 94-20367 Filed 8-15-94; 3:58 pm]

BILLING CODE 6351-01-M

COMMODITY FUTURES TRADING COMMISSION

TIME AND PLACE: 11:00 a.m., Friday,
September 9, 1994.

PLACE: 2033 K St., N.W., Washington, D.C., 8th Floor Hearing Room.

STATUS: Closed.

MATTERS TO BE CONSIDERED: Surveillance Matters.

CONTACT PERSON FOR MORE INFORMATION:

Jean A. Webb, 254-6314.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 94-20368 Filed 8-15-94; 3:58 pm]

BILLING CODE 6351-01-M

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 11:00 a.m., Friday,
September 16, 1994.

PLACE: 2033 K St., N.W., Washington, D.C., 8th Floor Hearing Room.

STATUS: Closed.

MATTERS TO BE CONSIDERED: Surveillance Matters.

CONTACT PERSON FOR MORE INFORMATION:

Jean A. Webb, 254-6314.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 94-20369 Filed 8-15-94; 3:58 pm]

BILLING CODE 6351-01-M

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 11:00 a.m., Friday,
September 23, 1994.

PLACE: 2033 K St., N.W., Washington, D.C., 8th Floor Hearing Room.

STATUS: Closed.

MATTERS TO BE CONSIDERED: Surveillance Matters.

CONTACT PERSON FOR MORE INFORMATION:

Jean A. Webb, 254-6314.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 94-20370 Filed 8-15-94; 3:58 pm]

BILLING CODE 6351-01-M

COMMODITY FUTURES TRADING COMMISSION

TIME AND DATE: 11 a.m., Friday,
September 30, 1994.

PLACE: 2033 K St., NW., Washington, DC, 8th Floor Hearing Room.

STATUS: Closed.

MATTERS TO BE CONSIDERED: Surveillance Matters.

CONTACT PERSON FOR MORE INFORMATION:

Jean A. Webb, 254-6314.

Jean A. Webb,

Secretary of the Commission.

[FR Doc. 94-20371 Filed 8-15-94; 3:58 pm]

BILLING CODE 6351-01-M

BOARD OF GOVERNORS OF THE FEDERAL RESERVE SYSTEM

TIME AND DATE: 11 a.m., Monday, August 22, 1994.

PLACE: Marriner S. Eccles Federal Reserve Board Building, C Street entrance between 20th and 21st Streets, NW., Washington, DC 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Proposed end-user computing strategy within the Federal Reserve System.
2. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.
3. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION:

Mr. Joseph R. Coyne, Assistant to the Board; (202) 452-3204. You may call (202) 452-3207, beginning at approximately 5 p.m. two business days before this meeting, for a recorded announcement of bank and bank holding company applications scheduled for the meeting.

Dated: August 12, 1994.

Jennifer J. Johnson,

Deputy Secretary of the Board.

[FR Doc. 94-20251 Filed 8-15-94; 9:18 am]

BILLING CODE 6210-01-P

UNITED STATES POSTAL SERVICE BOARD OF GOVERNORS

Notice of a Meeting

The Board of Governors of the United States Postal Service, pursuant to its Bylaws (39 CFR Section 7.5) and the Government in the Sunshine Act (5 U.S.C. Section 552b), hereby gives notice that it intends to hold a meeting at 10:30 a.m. on Monday, August 29, 1994, and at 9 a.m. on Tuesday, August 30, 1994, in St. Louis, Missouri. The August 29 meeting, at which the Board will have an informational briefing on funding for Multiline Optical Character Readers (MOCR) is closed to the public [See 59 FR 40415, August 8, 1994].

The August 30 meeting is open to the public and will be held at the Ritz-Carlton Hotel, 100 Carondelet Plaza, St. Louis, in Salon II of the Ballroom. The Board expects to discuss the matters stated in the agenda which is set forth below. Requests for information about the meeting should be addressed to the Secretary for the Board, David F. Harris, at (202) 268-4800.

Agenda

Monday Session

August 29—10:30 a.m. (Closed)

1. Informational Briefing on MOCR Funding. (William J. Dowling, Vice President, Engineering.)

Tuesday Session

August 30—9 a.m. (Open)

1. Minutes of the Previous Meeting, August 1-2, 1994.
2. Remarks of the Postmaster General/Chief Executive Officer. (Marvin Runyon.)
3. Postal Rate Commission FY 1995 Budget. (Chairman Sam Winters.)
4. Fiscal Year 1995 Financing Plan. (Michael J. Riley, Chief Financial Officer, Senior Vice President.)
5. Tentative FY 1996 Appropriation Request. (Mr. Riley.)
6. Status Report on Chicago, New York City and Washington, DC, Mail Service. (William J. Good, John F. Kelly, and Henry A. Pankey Area Vice Presidents.)
7. Report on the Mid-West Area (William J. Brown, Vice President, Mid-West Area Operations.)
8. Tentative Agenda for the October 3-4, 1994, meeting in Seattle, Washington.

David F. Harris,

Secretary.

[FR Doc. 94-20323 Filed 8-15-94; 2:47 pm]

BILLING CODE 7710-12-M

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August 17, 1994

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1994
August 17, 1994

Part II

Nuclear Regulatory Commission

Operating Licenses, Amendments; No
Significant Hazards Considerations;
Biweekly Notices

UNITED STATES NUCLEAR REGULATORY COMMISSION

Biweekly Notice

Applications and Amendments to Facility Operating Licenses Involving No Significant Hazards Considerations

I. Background

Pursuant to Public Law 97-415, the U.S. Nuclear Regulatory Commission (the Commission or NRC staff) is publishing this regular biweekly notice. Public Law 97-415 revised section 189 of the Atomic Energy Act of 1954, as amended (the Act), to require the Commission to publish notice of any amendments issued, or proposed to be issued, under a new provision of section 189 of the Act. This provision grants the Commission the authority to issue and make immediately effective any amendment to an operating license upon a determination by the Commission that such amendment involves no significant hazards consideration, notwithstanding the pendency before the Commission of a request for a hearing from any person.

This biweekly notice includes all notices of amendments issued, or proposed to be issued from July 25, 1994, through August 5, 1994. The last biweekly notice was published on August 3, 1994.

Notice Of Consideration Of Issuance Of Amendments To Facility Operating Licenses, Proposed No Significant Hazards Consideration Determination, And Opportunity For A Hearing

The Commission has made a proposed determination that the following amendment requests involve no significant hazards consideration. Under the Commission's regulations in 10 CFR 50.92, this means that operation of the facility in accordance with the proposed amendment would not (1) involve a significant increase in the probability or consequences of an accident previously evaluated; or (2) create the possibility of a new or different kind of accident from any accident previously evaluated; or (3) involve a significant reduction in a margin of safety. The basis for this proposed determination for each amendment request is shown below.

The Commission is seeking public comments on this proposed determination. Any comments received within 30 days after the date of publication of this notice will be considered in making any final determination.

Normally, the Commission will not issue the amendment until the

expiration of the 30-day notice period. However, should circumstances change during the notice period such that failure to act in a timely way would result, for example, in derating or shutdown of the facility, the Commission may issue the license amendment before the expiration of the 30-day notice period, provided that its final determination is that the amendment involves no significant hazards consideration. The final determination will consider all public and State comments received before action is taken. Should the Commission take this action, it will publish in the **Federal Register** a notice of issuance and provide for opportunity for a hearing after issuance. The Commission expects that the need to take this action will occur very infrequently.

Written comments may be submitted by mail to the Rules Review and Directives Branch, Division of Freedom of Information and Publications Services, Office of Administration, U.S. Nuclear Regulatory Commission, Washington, DC 20555, and should cite the publication date and page number of this **Federal Register** notice. Written comments may also be delivered to Room 6D22, Two White Flint North, 11545 Rockville Pike, Rockville, Maryland from 7:30 a.m. to 4:15 p.m. Federal workdays. Copies of written comments received may be examined at the NRC Public Document Room, the Gelman Building, 2120 L Street, NW., Washington, DC 20555. The filing of requests for a hearing and petitions for leave to intervene is discussed below.

By September 16, 1994, the licensee may file a request for a hearing with respect to issuance of the amendment to the subject facility operating license and any person whose interest may be affected by this proceeding and who wishes to participate as a party in the proceeding must file a written request for a hearing and a petition for leave to intervene. Requests for a hearing and a petition for leave to intervene shall be filed in accordance with the Commission's "Rules of Practice for Domestic Licensing Proceedings" in 10 CFR Part 2. Interested persons should consult a current copy of 10 CFR 2.714 which is available at the Commission's Public Document Room, the Gelman Building, 2120 L Street, NW., Washington, DC 20555 and at the local public document room for the particular facility involved. If a request for a hearing or petition for leave to intervene is filed by the above date, the Commission or an Atomic Safety and Licensing Board, designated by the Commission or by the Chairman of the Atomic Safety and Licensing Board

Panel, will rule on the request and/or petition; and the Secretary or the designated Atomic Safety and Licensing Board will issue a notice of a hearing or an appropriate order.

As required by 10 CFR 2.714, a petition for leave to intervene shall set forth with particularity the interest of the petitioner in the proceeding, and how that interest may be affected by the results of the proceeding. The petition should specifically explain the reasons why intervention should be permitted with particular reference to the following factors: (1) the nature of the petitioner's right under the Act to be made a party to the proceeding; (2) the nature and extent of the petitioner's property, financial, or other interest in the proceeding; and (3) the possible effect of any order which may be entered in the proceeding on the petitioner's interest. The petition should also identify the specific aspect(s) of the subject matter of the proceeding as to which petitioner wishes to intervene. Any person who has filed a petition for leave to intervene or who has been admitted as a party may amend the petition without requesting leave of the Board up to 15 days prior to the first prehearing conference scheduled in the proceeding, but such an amended petition must satisfy the specificity requirements described above.

Not later than 15 days prior to the first prehearing conference scheduled in the proceeding, a petitioner shall file a supplement to the petition to intervene which must include a list of the contentions which are sought to be litigated in the matter. Each contention must consist of a specific statement of the issue of law or fact to be raised or controverted. In addition, the petitioner shall provide a brief explanation of the bases of the contention and a concise statement of the alleged facts or expert opinion which support the contention and on which the petitioner intends to rely in proving the contention at the hearing. The petitioner must also provide references to those specific sources and documents of which the petitioner is aware and on which the petitioner intends to rely to establish those facts or expert opinion. Petitioner must provide sufficient information to show that a genuine dispute exists with the applicant on a material issue of law or fact. Contentions shall be limited to matters within the scope of the amendment under consideration. The contention must be one which, if proven, would entitle the petitioner to relief. A petitioner who fails to file such a supplement which satisfies these requirements with respect to at least one

contention will not be permitted to participate as a party.

Those permitted to intervene become parties to the proceeding, subject to any limitations in the order granting leave to intervene, and have the opportunity to participate fully in the conduct of the hearing, including the opportunity to present evidence and cross-examine witnesses.

If a hearing is requested, the Commission will make a final determination on the issue of no significant hazards consideration. The final determination will serve to decide when the hearing is held.

If the final determination is that the amendment request involves no significant hazards consideration, the Commission may issue the amendment and make it immediately effective, notwithstanding the request for a hearing. Any hearing held would take place after issuance of the amendment.

If the final determination is that the amendment request involves a significant hazards consideration, any hearing held would take place before the issuance of any amendment.

A request for a hearing or a petition for leave to intervene must be filed with the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, DC 20555, Attention: Docketing and Services Branch, or may be delivered to the Commission's Public Document Room, the Gelman Building, 2120 L Street, NW., Washington DC 20555, by the above date. Where petitions are filed during the last 10 days of the notice period, it is requested that the petitioner promptly so inform the Commission by a toll-free telephone call to Western Union at 1-(800) 248-5100 (in Missouri 1-(800) 342-6700). The Western Union operator should be given Datagram Identification Number N1023 and the following message addressed to (Project Director): petitioner's name and telephone number, date petition was mailed, plant name, and publication date and page number of this Federal Register notice. A copy of the petition should also be sent to the Office of the General Counsel, U.S. Nuclear Regulatory Commission, Washington, DC 20555, and to the attorney for the licensee.

Nontimely filings of petitions for leave to intervene, amended petitions, supplemental petitions and/or requests for a hearing will not be entertained absent a determination by the Commission, the presiding officer or the Atomic Safety and Licensing Board that the petition and/or request should be granted based upon a balancing of factors specified in 10 CFR 2.714(a)(1)(i)-(v) and 2.714(d).

For further details with respect to this action, see the application for amendment which is available for public inspection at the Commission's Public Document Room, the Gelman Building, 2120 L Street, NW., Washington, DC 20555, and at the local public document room for the particular facility involved.

Arizona Public Service Company, et al.,
Docket Nos. STN 50-528, STN 50-529, and STN 50-530, Palo Verde Nuclear Generating Station, Unit Nos. 1, 2, and 3, Maricopa County, Arizona

Date of amendment requests: May 4, 1994

Description of amendment requests: These amendment requests would revise Limiting Condition for Operation (LCO) 3.4.8.3 and Surveillance Requirement 4.4.8.3.1, "Overpressure Protection Systems." Specifically, the LCO and surveillance requirements are revised to clarify that both shutdown cooling system (SCS) suction line relief valves shall be OPERABLE and aligned to provide overpressure protection not only during reactor (RCS) cooldown or heatup evolutions, but also during any steady state temperature periods maintained in the course of RCS cooldown or heatup evolutions.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensees have provided their analysis about the issue of no significant hazards consideration, which is presented below:

Standard 1 -- Involve a significant increase in the probability or consequence of an accident previously evaluated.

The proposed amendments provide further clarification of the Technical Specifications and represent an additional operating limitation. Incorporating the noted clarification will not change the bases or assumptions contained in the safety analysis for this system. The most limiting low-temperature overpressure protection (LTOP) transients, the starting of an idle reactor coolant pump (RCP) and the inadvertent actuation of two high pressure safety injection (HPSI) pumps into a solid RCS, are not affected by the proposed clarification. Therefore, the proposed amendments do not involve a significant increase in the probability or consequences of an accident previously evaluated.

Standard 2 -- Create the possibility of a new or different kind of accident from any accident previously evaluated.

Clarifying the applicability of the LCO's and surveillance for steady state periods achieved and maintained during either a heatup or cooldown evolution does not modify the design or operation of plant equipment. No new or different failure modes will be introduced by incorporating this clarification into the LCO and surveillance requirement. Therefore, the

proposed amendments will not create the possibility of a new or different kind of accident from any accident previously evaluated.

Standard 3 -- Involve a significant reduction in a margin of safety.

The clarification will enhance LCO 3.4.8.3 and Surveillance Requirement 4.4.8.3.1 for heatup and cooldown evolutions by ensuring operators are aware of this applicability during periods of steady state conditions. This clarification does not involve a change to safety limits, setpoints, or design margins. As such, the proposed amendments will not involve a significant reduction in a margin of safety at PVNGS.

The NRC staff has reviewed the licensees' analysis and, based on that review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment requests involve no significant hazards consideration.

Local Public Document Room location: Phoenix Public Library, 12 East McDowell Road, Phoenix, Arizona 85004

Attorney for licensees: Nancy C. Loftin, Esq., Corporate Secretary and Counsel, Arizona Public Service Company, P.O. Box 53999, Mail Station 9068, Phoenix, Arizona 85072-3999

NRC Project Director: Theodore R. Quay

Arizona Public Service Company, et al.,
Docket Nos. STN 50-528, STN 50-529, and STN 50-530, Palo Verde Nuclear Generating Station, Unit Nos. 1, 2, and 3, Maricopa County, Arizona

Date of amendment requests: June 17, 1994

Description of amendment requests: The proposed amendments would increase the minimum nitrogen accumulator pressure for the atmospheric dump valves (ADVs), as stated in the surveillance requirements of Technical Specification (TS) 3/4.7.1.6. The change to the Bases increases the minimum time the ADV accumulators must be operable.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensees have provided their analysis about the issue of no significant hazards consideration, which is presented below:

Standard 1 -- Involve a significant increase in the probability or consequences of an accident previously evaluated.

The proposed Technical Specification change in the nitrogen accumulator supply minimum pressure will not increase the probability or consequences of any accident previously analyzed. The nitrogen accumulator pressure is normally maintained between 650-680 psig. Nitrogen pressure from the accumulator is reduced to 105 psig

prior to use in the operation of the ADVs. The pressure reduction will remain the same with the higher minimum accumulator pressure.

Standard 2 -- Create the possibility of a new or different kind of accident from any accident previously evaluated.

Increasing the nitrogen accumulator minimum pressure does not create any new or different accidents than those previously evaluated. The normal air supply (the Instrument Air System) to the ADV is maintained between 105 to 125 psig. Currently, nitrogen from the accumulator is reduced to 105 psig prior to use in the ADV. The increased minimum pressure in the accumulator will still be reduced to 105 psig prior to use in the ADV.

Standard 3 -- Involve a significant reduction in a margin of safety.

The limitation on maintaining the nitrogen accumulator at a certain pressure is to ensure that a sufficient volume of nitrogen is in the accumulator to operate the associated ADV. Maintaining a higher minimum pressure ensures that sufficient nitrogen will be available to maintain the unit at HOT STANDBY for four hours and an additional 9.3 hours to reach COLD SHUTDOWN under natural circulation conditions in the event of failure of the normal control air system. Therefore, the proposed change does not involve a reduction in a margin of safety.

The NRC staff has reviewed the licensees' analysis and, based on that review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment requests involve no significant hazards consideration.

Local Public Document Room
location: Phoenix Public Library, 12 East McDowell Road, Phoenix, Arizona 85004

Attorney for licensees: Nancy C. Loftin, Esq., Corporate Secretary and Counsel, Arizona Public Service Company, P.O. Box 53999, Mail Station 9068, Phoenix, Arizona 85072-3999
NRC Project Director: Theodore R. Quay

Arizona Public Service Company, et al., Docket Nos. STN 50-528, STN 50-529, and STN 50-530, Palo Verde Nuclear Generating Station, Unit Nos. 1, 2, and 3, Maricopa County, Arizona

Date of amendment requests: July 12, 1994

Description of amendment requests: The proposed amendment would enhance the PVNGS Technical Specifications (TS) by adding a limiting condition for operation (LCO) action statement to Entry VIII B of Table 3.3-3, "Engineered Safety Features Actuation System Instrumentation." The proposed action statement would enhance safe plant operation by requiring timely plant shutdown if more than one of the new solid state degraded

voltage relays in either train of 4.16kV are inoperable or not energized.

Basis for proposed no significant hazards consideration determination:

As required by 10 CFR 50.91(a), the licensees have provided their analysis about the issue of no significant hazards consideration, which is presented below:

Standard 1--Involve a significant increase in the probability or consequence of an accident previously evaluated:

The proposed amendment will add an action statement to TS Table 3.3-3 entry VIII B which would allow eight hours to effect repairs. This action statement would be entered if more than one of the required four degraded voltage relays on either 4.16 kv bus is inoperable or not energized. If the eight hour allowed outage time is not met, the unit is placed in Hot Standby within six hours and in Cold Shutdown within the next thirty hours. Technical Specification 3.8.3.1 currently allows eight hours to restore a 4.16 kv bus in the event of a loss of power to that bus. The loss of degraded voltage relays on that bus does not impact plant nuclear safety any more than the loss of the bus itself. Furthermore, even with the loss of all four degraded voltage relays monitoring one 4.16 kv bus (for example, due to a blown 125 vdc circuit fuse), the loss-of-voltage relays on that bus, and the degraded voltage relays, as well as the loss-of-voltage relays monitoring the other bus would be unaffected. None of the UFSAR chapter 15 accident analyses are affected by this proposed amendment. The existing TS requirements and those components to which they apply are not altered by this TS amendment. There are no changes to the maintenance, surveillance, and/or qualification of any component/function in Table 3.3-3. Therefore, the addition of this proposed eight hour action statement to Table 3.3-3 entry VIII B does not increase the probability of occurrence or the consequences of any previously evaluated accident.

Standard 2--Create the possibility of a new or different kind of accident from any accident previously evaluated:

The TS requirements and the components to which they apply are not altered by this amendment. The new solid state degraded voltage relays in each 4.16 kv bus were installed under the 10 CFR 50.59 change process. APS [Arizona Public Service Company] determined that the installation created no unreviewed safety question. This amendment has no impact on plant maintenance, testing, shutdown equipment, or component qualification. Plant operational safety is enhanced by this amendment. Therefore, the possibility of a new or different kind of accident is not created by this amendment.

Standard 3--Involve a significant reduction in a margin of safety:

The TS does not alter existing TS requirements or those components to which they apply. More specifically, there is no impact on safe plant shutdown, maintenance, containment isolation capability, containment leakage rate, or the operability of safety related valves. Therefore, the

addition of the proposed action statement to the TS will not involve reduction in a margin of safety for fission product release to the atmosphere.

The NRC staff has reviewed the licensees' analysis and, based on that review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment requests involve no significant hazards consideration.

Local Public Document Room
location: Phoenix Public Library, 12 East McDowell Road, Phoenix, Arizona 85004

Basis for proposed no significant hazards consideration determination:

Attorney for licensees: Nancy C. Loftin, Esq., Corporate Secretary and Counsel, Arizona Public Service Company, P.O. Box 53999, Mail Station 9068, Phoenix, Arizona 85072-3999
NRC Project Director: Theodore R. Quay

Baltimore Gas and Electric Company, Docket Nos. 50-317 and 50-318, Calvert Cliffs Nuclear Power Plant, Unit Nos. 1 and 2, Calvert County, Maryland

Date of amendments request: June 8, 1994

Description of amendments request: The proposed amendment would revise the Calvert Cliffs Nuclear Power Plant (CCNPP) Units 1 and 2 Technical Specification (TS) Section 4.7.1.2.c to extend the interval for three Auxiliary Feedwater (AFW) surveillance requirements from 18 to 24 months. Specifically, TS Section 4.7.2.c.1 requires the verification of each automatic valve in the flowpath actuate to its correct position and each AFW pump automatically start upon receipt of each AFW actuation system test signal; TS Section 4.7.2.c.2 requires verification that the AFW system is capable of providing a minimum 300 gallons per minute nominal flow to each leg. This request is one of a series of proposed license amendments that would eliminate the need for mid-cycle surveillance outages by extending 18-month frequency surveillances to every refueling outage (nominally each 24 months).

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

1. Would not involve a significant increase in the probability or consequences of an accident previously evaluated.

The Auxiliary Feedwater (AFW) System provides a safety-related source of feedwater to the steam generators to mitigate design

basis accidents involving loss of Main Feedwater. Failure of the AFW System is not an initiator for any previously analyzed accident. Therefore, the proposed change does not involve an increase in the probability of an accident previously evaluated.

A historical review of surveillance test results and system performance indicates that the AFW System is very reliable. In addition, monthly surveillances of the AFW System will continue to verify proper pump and valve operation. The AFW System reliability and monthly surveillances provide assurance that undetected system degradation will not occur between 24-month surveillances. Therefore, the AFW System will continue to perform its safety function and there will be no significant increase in the consequences of accidents. Therefore, the proposed Technical Specification changes do not increase the probability or consequences of an accident previously evaluated.

2. Would not create the possibility of a new or different type of accident from any accident previously evaluated?

This requested revision to increase the interval for some AFW surveillances from 18 to 24 months does not involve a significant change in the design or operation of the plant. No hardware is being added to the plant as part of the proposed change. The proposed change will not introduce any new accident initiators. Therefore, this change would not create the possibility of a new or different type of accident from any accident previously evaluated.

3. Does operation of the facility in accordance with the proposed amendment involve a significant reduction in a margin of safety?

The AFW System provides a margin of safety by providing a safety-related alternate supply of feedwater to the steam generator for removal of decay heat and cooldown of the Reactor Coolant System. The proposed changes do not affect the operation or design of the AFW System. Monthly surveillances and historical data provide assurance that the reduction in surveillance frequency will not adversely affect our ability to detect degradation in the system. Therefore, the proposed change does not involve a significant reduction in a margin of safety.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendments request involves no significant hazards consideration.

Local Public Document Room location: Calvert County Library, Prince Frederick, Maryland 20678.

Attorney for licensee: Jay E. Silbert, Esquire, Shaw, Pittman, Potts and Trowbridge, 2300 N Street, NW., Washington, DC 20037.

NRC Project Director: Michael L. Boyle

Consolidated Edison Company of New York, Docket No. 50-247, Indian Point Nuclear Generating Unit No. 2, Westchester County, New York

Date of amendment request: April 29, 1994

Description of amendment request: This amendment is an additional followup to the amendment request of May 29, 1992, published in the *Federal Register* on July 8, 1992 (57FR30242), which changed the Technical Specifications Section 1.0, Definitions, to accommodate a 24-month fuel cycle and which proposed the extension of the test intervals for specific surveillance tests. This amendment proposes extending the surveillance intervals to 24 months for the following additional surveillance tests: (1) Calibrate and test channels for Auxiliary Feedwater (AFW) initiation on steam generator water level (low-low). (2) Test channels for Auxiliary Feedwater initiation on trip of main feedwater pumps. The licensee's amendment proposal of November 25, 1992, requested approval for extending the surveillance interval of the Auxiliary Feedwater System to accommodate a 24-month fuel cycle and the approved change was issued in License Amendment No. 166. Subsequently, the licensee determined that two additional surveillances associated with this system had not been identified in the November 25, 1992, request. This amendment proposal requests approval of the additional surveillances. The changes requested by the licensee are in accordance with Generic Letter 91-04, "Changes in Technical Specification Surveillance Intervals to Accommodate a 24-Month Fuel Cycle."

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

The proposed change does not involve a significant hazards consideration since:

1. There is no significant increase in the probability or consequences of an accident.

The test results over the last four refuelings confirmed system operability with only one failure. This failure would not have impaired the ability of the auxiliary feedwater system to perform its intended safety function. The auxiliary feedwater system is redundant and diverse. The failure in the turbine driven pump did not impact the motor driven pumps.

Based on the historical test data, it is concluded that no significant increase in the probability or consequences of an accident would be incurred by extending the operating cycle due to an increased surveillance interval.

2. The possibility of a new or different kind of accident from any previously analyzed has not been created.

The failure noted from the past test data appears random in nature and would not have defeated the redundancy in design that exists in the AFW system. The AFW system would have been capable of performing its intended safety function and therefore a new or different kind of accident would not have been created.

3. There has been no reduction in the margin of safety.

Past historical data demonstrates that the AFW systems would perform their safety function for an extended operating cycle should the surveillance period be extended by several months.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610.

Attorney for licensee: Brent L. Brandenburg, Esq., 4 Irving Place, New York, New York 10003.

NRC Project Director: Pao Tsin Kuo

Consolidated Edison Company of New York, Docket No. 50-247, Indian Point Nuclear Generating Unit No. 2, Westchester County, New York

Date of amendment request: June 16, 1994

Description of amendment request: The proposed amendment would revise License Condition 2.K of the license issued August 24, 1981, to provide for compliance with the NRC-approved fire protection program as described in the Updated Final Safety Analysis Report and for making changes to the NRC-approved fire protection program; would delete fire protection Technical Specification (TS) Sections 3.13 and 4.14 which contain limiting conditions for operation and surveillance requirements, respectively, for the high-pressure water fire protection system, fire protection spray systems, penetration fire barriers, fire detection systems, fire hose stations and hydrants, and the cable spreading room halon system; would delete Section 6.2.2.f which contains fire brigade staffing requirements; would delete Section 6.4.2 which contains fire brigade training requirements; would add Section 6.5.1.6.1 to add fire protection program responsibilities to the Station Nuclear Committee; would add Section 6.8.1.e to require written procedures and administrative policies for the fire protection program; would delete

Section 6.9.2.b which requires a Special Report for inoperable fire protection and detection equipment; and would make corresponding changes to the Table of Contents and List of Tables.

Generic Letter (GL) 86-10, dated April 24, 1986, and GL 88-12, dated August 2, 1988, from the NRC provided guidance to licensees to request removal of the fire protection TS. The licensee's proposed amendment is in response to these GLs.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

The Commission has provided guidance concerning the application of the standards for determining whether a "Significant Hazards Consideration" exists by providing certain examples in 51 FR 7744 (dated March 6, 1986). Example (vii) of those involving no significant hazards considerations relates to "a change to conform a license to changes in the regulations, where the license change results in very minor changes to facility operations clearly in keeping with the regulations."

In this case, NRC Generic Letters 86-10 and 88-12, although not regulations, provide pertinent guidance relative to the above described proposed changes and implementation of the NRC fire protection regulations of 10 CFR 50.48(a). Specifically, the generic letters allow licensees to delete fire protection related technical specifications, provided that administrative requirements are added to technical specifications and a license condition is provided that requires the implementation and maintenance in effect of the approved fire protection program. Further, the generic letters provide for inclusion of the fire protection program into the UFSAR [Updated Final Safety Analysis Report] and permits future changes to the fire protection program without prior NRC approval, all as provided by the license condition and in accordance with the provisions of 10 CFR 50.59. Therefore, since the actions required by the generic letters have been taken and conform the license to the current interpretation of NRC fire protection regulations as described in Generic Letters 86-10 and 88-12, with no changes to facility operations, these proposed changes are in accordance with Example (vii) above.

In accordance with the requirements of 10 CFR 50.92, the proposed changes to the Technical Specifications are deemed not to involve any "Significant Hazards Considerations" because operation of Indian Point Unit No. 2 in accordance with these changes would not:

(1) Involve a significant increase in the probability or consequences of an accident previously evaluated.

The fire protection program requirements are not affected in that the function, operation or surveillance requirements for any fire protection system or component are

not being altered. The proposed changes simply relocate these requirements from the Technical Specifications to the UFSAR, are administrative in nature, and do not affect any other current plant equipment or practices. Therefore, the conclusions of current accident analyses are not affected. Further, as permitted by the proposed License Condition 2.K, changes in the NRC-approved fire protection program will require an evaluation per the criteria of 10 CFR 50.59 to determine that the proposed change will not involve an unreviewed safety question. Therefore, future changes to the fire protection program will be evaluated in accordance with appropriate criteria.

(2) Create the possibility for a new or different kind of accident from any previously evaluated.

The proposed changes introduce no new mode of plant operation, do not involve physical modification to any structure, system or component, do not affect the function, operation or surveillance requirements for any equipment necessary for safe operation or shutdown of the plant, or of fire protection equipment which protects such equipment, and do not involve any changes to setpoints or operating parameters. The changes are administrative only and all existing fire protection requirements are maintained. Therefore, the changes can not result in an unanalyzed accident. Further, as permitted by the proposed License Condition 2.K, changes in the NRC-approved fire protection program will require an evaluation per the criteria of 10 CFR 50.59 to determine that the proposed change will not involve an unreviewed safety question. Therefore, future changes to the fire protection program will be evaluated in accordance with appropriate criteria.

(3) Involve a significant reduction in the margin of safety.

The existing fire protection program operability and surveillance requirements are retained as they are contained in the FPPP [Fire Protection Program Plan], and compliance will continue through proposed License Condition 2.K. Therefore, no margins of safety established by design or verified by testing to ensure operability of fire protection systems or components are affected. Further, as permitted by the proposed License Condition 2.K, changes in the NRC-approved fire protection program will require an evaluation per the criteria of 10 CFR 50.59 to determine that the proposed change will not involve an unreviewed safety question. Therefore, future changes to the fire protection program will be evaluated in accordance with appropriate criteria.

Based on the above discussion, since these proposed changes to the Indian Point Unit No. 2 Technical Specifications satisfy the criteria specified in 10 CFR 50.92, are similar to an example provided by the Commission of a change which involves "No Significant Hazards Considerations", and are not similar to any examples that involve a "Significant Hazards Consideration", Con Edison has determined that this amendment application does not involve any "Significant Hazards Considerations."

The proposed Technical Specification changes have been reviewed by the Station

Nuclear Safety Committee and the Con Edison Nuclear Facilities Safety Committee. Both committees concur that these proposed changes do not represent any "Significant Hazards Considerations."

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610.

Attorney for licensee: Brent L. Brandenburg, Esq., 4 Irving Place, New York, New York 10003.

NRC Project Director: Michael L. Boyle

Consolidated Edison Company of New York, Docket No. 50-247, Indian Point Nuclear Generating Unit No. 2, Westchester County, New York

Date of amendment request: July 8, 1994

Description of amendment request: The proposed amendment would revise Technical Specification Section 3.7, Auxiliary Electrical Systems to clarify offsite power availability requirements and to revise emergency diesel generator fuel oil availability requirements.

Basis for proposed no significant hazards consideration determination. As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

Consistent with the requirements of 10 CFR 50.92, the enclosed application involves no significant hazards based on the following information:

1) Does the proposed license amendment involve a significant increase in the probability or consequences of an accident previously evaluated?

Response: Neither the probability nor the consequence of an accident previously analyzed is increased due to the proposed changes. There are no changes on the existing offsite power supply configuration or on the existing diesel fuel oil supply system or inventory requirements. This proposed amendment will allow for three diesel operation when a fuel oil storage tank or transfer pump is unavailable. In the event of an accident at this time, the three diesel operation would allow for more than minimum safeguards to be available, with maximum safeguards available for the first part of the event.

2) Does the proposed license amendment create the possibility of a new or different kind of accident from any previously evaluated?

Response:

The existing 138 kV and 13.8 kV offsite power reliability is maintained with this change. There is no impact on availability of the alternate AC system, the three gas turbines, with this change. This change is consistent with the original licensing basis that the AEC accepted for the diesel fuel oil supply system.

3) Does the proposed amendment involve a significant reduction in the margin of safety?

Response:

The proposed amendment does not involve a significant reduction in the margin of safety. The proposed amendment maintains the reliability of the preferred 138 kV and 13.8 kV offsite power and is consistent with the original licensing basis for diesel fuel oil inventory.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room

location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610.

Attorney for licensee: Brent L. Brandenburg, Esq., 4 Irving Place, New York, New York 10003.

NRC Project Director: Robert A. Capra

Duquesne Light Company, et al., Docket No. 50-334, Beaver Valley Power Station, Unit No. 1, Shippingport, Pennsylvania

Date of amendment request: July 29, 1994

Description of amendment request:

The proposed amendment would revise Technical Specifications (TSs) 3/4.4.5 and 3/4.4.6.2 and associated bases to allow the implementation of interim steam generator tube plugging criteria for the tube support elevations during cycle 11. The allowed primary-to-secondary operational leakage from any one steam generator is proposed to be reduced from 500 gallons per day (gpd) to 150 gpd. The total allowed primary-to-secondary operational leakage from all steam generators would be reduced from one gallon per minute (1440 gpd) to 450 gpd.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

1. Does the change involve a significant increase in the probability or consequences of an accident previously evaluated?

Testing of model boiler specimens for free span tubing (no tube support plate [TSP] restraint) at room temperature conditions

show[s] burst pressures in excess of 5000 psi for indications of outer diameter stress corrosion cracking with voltage measurement as high as 19 volts. Burst testing performed on intersections pulled from BVPS [Beaver Valley Power Station] with up to a 2.7 volt indication shows measured burst pressure in excess of 6600 psi at room temperature. Burst testing performed on pulled tubes from other plants with up to 7.5 volt indications show[s] burst pressures in excess of 6300 psi at room temperatures. Correcting for the effects of temperature on material properties and minimum strength levels (as the burst testing was done at room temperature), tube burst capability significantly exceeds the safety factor requirements of RG [Regulatory Guide] 1.121. As stated earlier, tube burst criteria are inherently satisfied during normal operating conditions due to the proximity of the TSP. Test data indicates that tube burst cannot occur within the TSP, even for tubes which have 100 percent through wall electric discharge machining (EDM) notches, 0.75 inch long, provided that the TSP is adjacent to the notched area. Since tube to TSP proximity precludes tube burst during normal operating conditions, use of the criteria must retain tube integrity characteristics which maintain a margin of safety of 1.43 times the bounding faulted condition steam line break (SLB) pressure differential. As previously stated, the RG 1.121 criterion requiring maintenance of a safety factor of 1.43 times the SLB pressure differential on tube burst is satisfied by 7/8 inch diameter tubing with bobbin coil indications with signal amplitudes less than 8.82 volts regardless of the indicated depth measurement. The plugging criteria (resulting in a projected end-of-cycle [EOC] voltage) compares favorably with the 8.82 volt structural limit considering the extremely slow apparent voltage growth rate of indications at BVPS. Using the established methodology of RG 1.121, the structural limit is reduced by allowances for uncertainty and growth to develop a beginning-of-cycle (BOC) repair limit which should preclude indications at EOC conditions which exceed the structural limit. The non-destructive examination (NDE) uncertainty component is 20.5 percent and is based on the EPRI [Electric Power Research Institute] Alternate Repair Criteria (ARC). A bounding growth allowance of 40 percent will be applied. This value is conservative for BVPS Unit 1. The BOC maximum allowable repair limit should not permit the existence of EOC indications (when the 40 percent growth and 20.5 percent uncertainty allowances are applied) which exceed the 8.82 volt structural limit. By adding NDE uncertainty allowances and an allowance for crack growth to the repair limit, the structural limit can be validated. Therefore, the maximum allowable BOC repair limit (RL) based on the structural limit of 8.82 volts can be represented by the expression:

$$RL + (0.205 \times RL) + (0.40 \times RL) = 8.82 \text{ volts, or the maximum allowable BOC repair limit can be expressed as:}$$

$$RL = 8.82 \text{ volt structural limit} / 1.605 = 5.5 \text{ volts.}$$

It is reasonable that this repair limit (5.5 volts) could be applied for IPC [interim

plugging criterion] implementation to repair bobbin indications greater than 1.0 or 2.0 volts independent of RPC [rotating pancake coil] confirmation of the indication. The analyses were performed based on a 1.0 or 2.0 volt repair limit. Duquesne Light Company has chosen to use a steam generator tube repair limit of 1.0 volt. Conservatively, an upper limit of 3.6 volts will be used to assess tube integrity for those bobbin indications which are above 1.0 volt but do not have confirming RPC calls. This 3.6 volt upper limit for non-confirmed RPC calls is consistent with other recently approved IPC programs for the two other plants with 7/8 inch tubing that currently implement IPCs. Since the upper bound for repair of non-confirmed RPC is limited to a value far less than the limit associated with a full alternate criteria, the establishment of the repair limits are [is] judged to be independent of the pulled tube data base used.

The conservatism of the growth allowance used to develop the repair limit is shown by the most recent BVPS eddy current data. The average voltage growth for all indications was 16 percent while the average voltage growth for indications greater than 0.75 volts at BOC was 6 percent. The largest overall voltage growth in a particular steam generator was found in the "A" steam generator, which had an overall average growth of 25 percent. Only two tubes had an absolute voltage growth which exceeded 1.0 volt for Cycle 9. The maximum absolute voltage growth in the 1993 inspection was recorded to be 1.18 volts. Each of the last three inspections, which included 100 percent of all hot leg tubes, showed decreasing voltage growth trends in each successive inspection for all categories; overall voltage growth, growth of BOC indications less than 0.75 volts, and growth of indications greater than 0.75 volts. The decreasing voltage growth rate trend data indicates that DLC has good control of the ODSCC [outer diameter stress corrosion cracking] occurring in the BVPS Unit 1 steam generators and also implies that atypical voltage growth of a few indications is unlikely.

Relative to the expected leakage during accident condition loadings, it has been previously established that a postulated main SLB [steam line break] outside of containment but upstream of the main steam isolation valve (MSIV) represents the most limiting radiological condition relative to the IPC. In support of implementation of the interim plugging criteria, it will be determined whether the distribution of cracking indications at the TSP intersections at the end of Cycle 11 are [is] projected to be such that primary-to-secondary leakage would result in site boundary doses within a small fraction of the 10 CFR 100 guidelines. A separate calculation has determined this allowable SLB leakage limit to be 6.6 gpm in the faulted loop. This limit was calculated using the Technical Specification RCS [reactor coolant system] Iodine-131 activity level of 1.0 micro Curies per gram dose equivalent Iodine-131 and the recommended Iodine-131 transient spiking values consistent with NUREG-0800. The projected SLB leakage rate calculation methodology prescribed in Section 3.3 of draft NUREG-

1477 will be used to calculate EOC leakage. The log-logistic probability of leakage correlation will be used to establish the SLB leak rate used for comparison with the 6.6 gpm faulted loop allowable limit. Due to the relatively low voltage levels of indications at BVPS and low voltage growth rates, it is expected that the actual calculated leakage values will be far less than this limit. Additionally, the current Iodine-131 levels as of May 1994 at BVPS are about 1000 times less than the Technical Specification limit of 1.0.

Application of the criteria requires the projection of postulated SLB leakage, based on the projected EOC voltage distribution for the upcoming cycle. Projected EOC voltage distribution is developed using the most recent EOC eddy current results and a voltage measurement uncertainty. Data indicate that a threshold voltage of 2.8 volts would result in through wall cracks long enough to leak at steam line break conditions. Draft NUREG-1477 requires that all indications to which the IPC are applied must be included in the leakage projection. Tube pull results from another plant with 7/8 inch tubing with a substantial voltage growth data base have shown that tube wall degradation of greater than 40 percent through wall was readily detectable either by the bobbin or RPC probe. The tube with maximum through wall penetration of 56 percent (42 percent average) had a voltage of 2.02 volts. This indication also was the largest recorded bobbin voltage from the EOC eddy current data. Based on the BVPS pulled tube and industry pulled tube data supporting a lower threshold for SLB leakage of 2.8 volts, inclusion of all IPC intersections in the leakage model is quite conservative. The ODSCC occurring at BVPS has historically resulted in relatively low voltage levels and has exhibited decreasing voltage growth trends over the last three inspections. BVPS has not identified ODSCC as a contributor to operational leakage. The current leakage levels at BVPS are negligible (less than 1 gpd). In order to satisfy the requirements of draft NUREG-1477, EOC 10 eddy current data will be used to calculate the projected SLB leakage according to draft NUREG-1477 methodology. Leakage calculated using the recommended EPRI leakage correlation will also be provided. Duquesne Light Company is requesting that the NRC review and approve the EPRI SLB leakage calculation methodology. Sufficient justification is included to establish acceptability of the EPRI leakage correlation based on criteria provided by the NRC in the February 8, 1994, Industry/NRC working meeting on the voltage based criteria.

In order to assess the sensitivity of application of the voltage based criteria upon SLB leakage, the EOC 9 eddy current results were used to calculate postulated EOC 10 leakage using both the NUREG-1477 methodology and EPRI correlation assuming that a 1.0 or 2.0 volt plugging limit were implemented at the BOC 10.

Results indicate SLB leakage of 0.46 gpm and 0.044 gpm using the NUREG and EPRI methodologies with an assumed probability of detection (POD) of 0.6 for a 2.0 volt repair limit. Since Duquesne Light Company has

chosen to limit the voltage based plugging limit at 1.0 volt, EOC 11 SLB leakage is analyzed to be approximately 5 percent lower than the calculated SLB leakage with a 2.0 volt repair limit.

Therefore, implementation of the interim plugging criteria does not adversely affect steam generator tube integrity and implementation will be shown to result in acceptable dose consequences, therefore, the proposed amendment does not result in any increase in the probability or consequences of an accident previously evaluated.

2. Does the change create the possibility of a new or different kind of accident from any accident previously evaluated?

Implementation of the proposed steam generator tube interim TSP plugging criteria does not introduce any significant changes to the plant design basis. Use of the criteria does not provide a mechanism which could result in an accident outside of the region of the TSP elevations; no ODSCC that has been identified at the TSP has been detected outside the thickness of the TSPs. Neither a single or multiple tube rupture event would be expected in a steam generator in which the plugging criteria has been applied (during all plant conditions).

Specifically, Duquesne Light Company will implement a maximum leakage rate limit of 150 gpd per steam generator to help preclude the potential for excessive leakage during all plant conditions. The technical specification limits on primary-to-secondary leakage at operating conditions are to be a maximum of 450 gpd for all steam generators, or, a maximum of 150 gpd for any one steam generator. The RG 1.121 criterion for establishing operational leakage rate limits that require plant shutdown are based upon leak-before-break considerations to detect a free span crack before potential tube rupture during faulted plant conditions. The 150 gpd limit should provide for leakage detection and plant shutdown in the event of the occurrence of an unexpected single crack resulting in leakage that is associated with the longest permissible crack length. RG 1.121 acceptance criteria for establishing operating leakage limits are based on leak-before-break considerations such that plant shutdown is initiated if the leakage associated with the longest permissible crack is exceeded.

The single through wall crack lengths that result in tube burst at 1.43 times the steam line break pressure differential and SLB pressure differential alone are approximately 0.57 inch and 0.84 inch, respectively. A leak rate of 150 gpd will provide for detection of 0.41 inch long cracks at nominal leak rates and 0.62 inch long cracks at the lower 95 percent confidence level leak rates. Since tube burst is precluded during normal operation due to the proximity of the TSP to the tube and the potential exists for the crevice to become uncovered during SLB conditions, the leakage from the maximum permissible crack must preclude tube burst at SLB conditions. Thus, the 150 gpd limit provides for plant shutdown prior to reaching critical crack lengths for SLB conditions using the lower 95 percent leakage data. Additionally, this leak-before-break evaluation assumes that the entire

crevice area is uncovered during blowdown. Partial uncovering will provide benefit to the burst capacity of the intersection. Analyses have shown that only a small percentage of the TSPs are deflected greater than the TSP thickness during a postulated SLB.

Steam generator tube integrity continues to be maintained through inservice inspection and primary-to-secondary leakage monitoring, therefore, the possibility of a new or different kind of accident from any accident previously developed is not created.

3. Does the change involve a significant reduction in a margin of safety?

The use of the voltage based bobbin probe interim TSP elevation plugging criteria is demonstrated to maintain steam generator tube integrity commensurate with the requirements of RG 1.121. RG 1.121 describes a method acceptable to the NRC staff for meeting GDCs 14, 15, 31, and 32 by reducing the probability or the consequences of steam generator tube rupture. This is accomplished by determining the limiting conditions of degradation of steam generator tubing, as established by inservice inspection, for which tubes with unacceptable cracking should be removed from service. Upon implementation of the criteria, even under the worst case conditions, the occurrence of ODSCC at the TSP elevations is not expected to lead to a steam generator tube rupture event during normal or faulted plant conditions. The EOC distribution of crack indications at the TSP elevations will be confirmed to result in acceptable primary-to-secondary leakage during all plant conditions and that radiological consequences are not adversely impacted.

In addressing the combined effects of loss of coolant accident (LOCA) and safe shutdown earthquake (SSE) on the steam generator component (as required by GDC 2), it has been determined that tube collapse may occur in the steam generators at some plants. This is the case as the TSP may become deformed as a result of lateral loads at the wedge supports at the periphery of the plate due to the combined effects of the LOCA rarefaction wave and SSE loadings. Then, the resulting pressure differential on the deformed tubes may cause some of the tubes to collapse.

There are two issues associated with steam generator tube collapse. First, the collapse of steam generator tubing reduces the RCS flow area through the tubes. The reduction in flow area increases the resistance to flow of steam from the core during a LOCA which, in turn, may potentially increase peak clad temperature (PCT). Second, there is a potential that partial through wall cracks in tubes could progress to through wall cracks during tube deformation or collapse.

Consequently, since the leak-before-break methodology is applicable to the BVPS reactor coolant loop piping, the probability of breaks in the primary loop piping is sufficiently low that they need not be considered in the structural design of the plant. The limiting LOCA event becomes either the accumulator line break or the pressurizer surge line break. LOCA loads for the primary pipe breaks were used to bound the conditions at BVPS for smaller breaks. The results of the analysis using the larger

break inputs show that the LOCA loads were found to be of insufficient magnitude to result in steam generator tube collapse or significant deformation. The LOCA and SSE tube collapse evaluation performed for another plant with Series 51 steam generators using bounding input conditions (large break loadings) is considered applicable to BVPS.

Addressing RG 1.83 considerations, implementation of the bobbin probe voltage based interim tube plugging criteria is supplemented by: enhanced eddy current inspection guidelines to provide consistency in voltage normalization, a 100 percent eddy current inspection sample size at the TSP elevations, and RPC inspection requirements for the larger indications left in service to characterize the principal degradation as ODSCC.

As noted previously, implementation of the TSP elevation plugging criteria will decrease the number of tubes which must be repaired. The installation of steam generator tube plugs reduces the RCS flow margin. Thus, the implementation of the alternate plugging criteria will maintain the margin of flow that would otherwise be reduced in the event of increased tube plugging.

Based on the above, it is concluded that the proposed license amendment request does not result in a significant reduction in margin with respect to plant safety as defined in the Final Safety Analysis Report or any Bases of the Technical Specifications.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room
location: B. F. Jones Memorial Library,
663 Franklin Avenue, Aliquippa,
Pennsylvania 15001.

Attorney for licensee: Gerald Charnoff,
Esquire, Jay E. Silberg, Esquire, Shaw,
Pittman, Potts & Trowbridge, 2300 N
Street, NW., Washington, DC 20037.

NRC Project Director: Walter R.
Butler, Director

Entergy Operations, Inc., Docket Nos.
50-313, Arkansas Nuclear One, Unit 1,
Pope County, Arkansas

Date of amendment request: June 22,
1994

Description of amendment request:
The proposed amendment revises
technical specifications (TSs) related to
the emergency feedwater system (EFW).
The proposed changes extend the
allowable outage time when one EFW
train is inoperable from 36 hours to 72
hours and adapt other EFW sections
from the "Restructured Standard
Technical Specifications for B&W
Plants" to the Arkansas Nuclear One,
Unit 1 (ANO-1) format.

**Basis for proposed no significant
hazards consideration determination:**

As required by 10 CFR 50.91(a), the
licensee has provided its analysis of the
issue of no significant hazards
consideration, which is presented
below:

**Criterion 1 - Does Not Involve a Significant
Increase in the Probability or Consequences
of an Accident Previously Evaluated.**

The Emergency Feedwater (EFW) system
mitigates the consequences of any event with
a loss of normal feedwater. This system is not
the initiator of any previously analyzed
accident, and therefore, changes to the
specifications applicable to the EFW system
present no significant increase in the
probability of any previously evaluated
accident.

The changes that revise the required
Actions and Allowable Outage Times
associated with the EFW system have been
evaluated for their effect on the Core Damage
Frequency (CDF) previously calculated in the
ANO-1 Probabilistic Risk Assessment (PRA).
The new ANO-1 CDF values, incorporating
the proposed AOT extension, are 4.73E-05
(for the turbine-driven EFW pump) and
4.70E-05 (for the motor-driven pump). These
values do not exceed the NRC Safety Goal of
1.0E-04 per reactor year, as stated in the
Federal Register 50FR32138. The delta CDF
associated with these changes (6.16E-07 for
the turbine-driven EFW pump and 3.04E-07
for the motor-driven EFW pump) have been
evaluated with respect to criteria contained
in SECY-91-270, dated August 27, 1991, and
NUMARC 91-04, dated January 1992, and fall
within the category of events of low risk
significance requiring no compensatory
measures. This evaluation has shown the risk
associated with the proposed changes to pose
no undue risk to public health and safety, to
be categorized as having low risk
significance, and involve no significant
increase in the consequences of an accident
previously evaluated.

The changes revising the Limiting
Conditions for Operation result in more
restrictive controls on the operability of the
motor-driven EFW pump. The previous
specification required operability of both
EFW pumps when the reactor was heated
above 280°F. The proposed change requires
the operability of the motor-driven EFW
pump whenever the unit is above the cold
shutdown condition and any steam generator
is relied upon for heat removal. With this
change, the motor-driven EFW pump is now
required to be operable in a condition not
previously specified, constituting an
additional requirement not previously
specified. This change does not involve a
significant increase in the consequences of an
accident previously evaluated.

The changes revising the Limiting
Conditions for Operation also incorporate an
Allowable Outage Time for the turbine-
driven EFW pump steam supply valves
which was not previously specified. The 7
day AOT is reasonable based on:

1. The redundant steam supply (from the
opposite steam generator) to the turbine-
driven EFW pump is operable,
2. The motor-driven EFW pump is
operable, and

3. The probability of an event occurring
that would require the inoperable steam
supply valve to actuate is relatively low.

The changes to the surveillance
specifications clarify the proper conditions
required for the operability test of the
turbine-driven EFW pump, and revise the
requirement for the verification of proper
EFW flow path valve alignment. The change
clarifying the test conditions is required to
ensure a sufficient steam supply to the
turbine-driven EFW pump to perform the
test. During plant startup, from an RCS
temperature of 280°F to an RCS temperature
of approximately 525°F (corresponding to a
steam generator pressure of approximately
830 psig) the turbine-driven EFW pump is
classified as available until operability is
proven by successful completion of the
surveillance requirement. The proposed
changes state that the EFW pumps and their
associated flow paths shall be operable when
the RCS is above the cold shutdown
condition with any steam generator relied
upon for heat removal (motor-driven EFW
pump) and when RCS temperature is greater
than or equal to 280°F (turbine-driven EFW
pump). This specification requires that the
flow paths be properly aligned to maintain
operability and is as restrictive as the current
TS 4.3.1.c. The revised specification
incorporates a new requirement to verify
operator flexibility in determining the
method of verification. Some methods that
could be considered as fulfilling this
requirement would include valve alignment
checks, or a flow test verifying a level
decrease in the 'Q' condensate storage tank
with a corresponding level increase in both
steam generators. These changes result in no
significant increase in the consequences of an
accident previously evaluated.

The other proposed changes included in
this submittal, including the Bases changes,
are considered to be administrative in nature
and have no effect on the consequences of an
accident previously evaluated. Relocation of
the Emergency Feedwater Initiation and
Control (EFIC) requirements from Section 3.4
to Section 3.5 places the requirements for
this instrumentation system with the
requirements for other instrumentation
systems, resulting in greater consistency
throughout the ANO-1 TS. Information in the
Bases associated with the EFIC system has
been corrected to reflect the actual plant
condition and resolve a conflict with the
ANO-1 Safety Analysis Report. The Bases
changes add clarifying information to aid the
operator in determining the applicability of
the various EFW specifications.

Therefore, this change does not involve a
significant increase in the probability or
consequences of any accident previously
evaluated.

**Criterion 2 - Does Not Create the Possibility
of a New or Different Kind of Accident from
any Previously Evaluated.**

The proposed changes introduce no new
mode of plant operation. The EFW system is
not an event initiator. It functions to mitigate
the consequences of any event with a loss of
normal feedwater.

Therefore, this change does not create the
possibility of a new or different kind of
accident from any previously evaluated.

Criterion 3 - Does Not Involve a Significant Reduction in the Margin of Safety.

The changes proposed to the Limiting Conditions for Operation associated with the EFW system are more conservative than the current specification, thus resulting in an increase in the margin of safety. The proposed changes to the actions required when both of the EFW trains are inoperable and the auxiliary feedwater pump is unavailable no longer require an immediate plant runback, that is currently required, which could introduce a plant transient, thus resulting in an increase in the margin of safety.

The changes revising the Limiting Conditions for Operations also incorporate and Allowable Outage Time for the turbine-driven EFW pump steam supply valves which was not previously specified. The 7 day AOT is reasonable based on:

1. The redundant steam supply (from the opposite steam generator) to the turbine-driven EFW pump is operable,

2. The motor-driven EFW pump is operable, and

3. The probability of an event occurring that would require the inoperable steam supply valve to actuate is relatively low.

The changes to the surveillance specifications clarify the proper conditions required for the operability test of the turbine-driven EFW pump, and revise the requirement for the verification of proper EFW flow path valve alignment. The change clarifying the test conditions is required to ensure a sufficient steam supply to the turbine-driven EFW pump to perform the test. During plant startup, from an RCS temperature of 280°F to an RCS temperature of approximately 525°F (corresponding to a steam generator pressure of approximately 830 psig) the turbine-driven EFW pump is classified as available until operability is proven by successful completion of the surveillance requirement. The proposed changes state that the EFW pumps and their associated flow paths shall be operable when the RCS is above the cold shutdown condition with any steam generator relied upon for heat removal (motor-driven EFW pump) and when RCS temperature is greater than or equal to 280°F (turbine-driven EFW pump). This specification requires that the flow paths be properly aligned to maintain operability and is as restrictive as the current TS 4.8.1.c. The revised specification incorporates a new requirement to verify proper alignment prior to relying upon any steam generator for heat removal. This allows the operator flexibility in determining the method of verification. Some methods that could be considered as fulfilling this requirement would include manual valve alignment checks, or a flow test verifying a level decrease in the 'Q' condensate storage tank with a corresponding level increase in both steam generators.

This change does involve an incremental reduction in the margin of safety since the extension of the EFW Allowable Outage Time from 36 hours to 72 hours does result in a slight increase in the Core Damage Frequency (CDF) as calculated in the ANO-1 Probabilistic Risk Assessment. The new ANO-1 CDF values, incorporating the

proposed AOT extension, are 4.73E-05 (for the turbine-driven EFW pump) and 4.70E-05 (for the motor-driven EFW pump). These values do not exceed the NRC Safety Goal of 1.0E-04 per reactor year, as stated in the Federal Register 50FR32138. The CDF associated with these changes (6.16E-07 for the turbine-driven EFW pump and 3.04E-07 for the motor-driven EFW pump) have been evaluated with respect to criteria contained in SECY-91-270, dated August 27, 1991, and NUMARC 91-04, dated January 1992, and fall within the category of events of low risk significance requiring no compensatory measures. This reduction is not considered significant in that the increase in CDF has been evaluated as posing no undue risk to the public health and safety and is categorized as having low risk significance.

The other proposed changes included in this submittal, including the Bases changes, are considered to be administrative in nature. Relocation of the Emergency Feedwater Initiation and Control (EFIC) requirements from Section 3.4 to Section 3.5 places the requirements for this instrumentation system with the requirements for other instrumentation systems, resulting in greater consistency throughout the ANO-1 TS. Information in the Bases associated with the EFIC system has been corrected to reflect the actual plant condition and resolve a conflict with the ANO-1 Safety Analysis Report. The Bases changes add clarifying information to aid the operator in determining the applicability of the various EFW specifications.

Therefore, this change does not involve a significant reduction in the margin of safety.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room
location: Tomlinson Library, Arkansas
Tech University, Russellville, Arkansas
72801

Attorney for licensee: Nicholas S. Reynolds, Esquire, Winston and Strawn,
1400 L Street, N.W., Washington, D.C.
20005-3502

NRC Project Director: William D. Beckner

Entergy Operations, Inc., Docket Nos.
50-313 and 50-368, Arkansas Nuclear
One, Unit Nos. 1 and 2 (ANO-1&2),
Pope County, Arkansas

Date of amendment request: June 20, 1994

Description of amendment request:
The proposed amendments revise the administrative and control sections of the technical specifications (TSs) for Arkansas Nuclear One, Units 1 and 2. The proposed changes relocate controls associated with the "Review and Audit" functions from the TSs to the Quality Assurance Program and relocate

requirements for the audit of emergency and security plans and implementing procedures from the TSs to the respective emergency and security plans.

Basis for proposed no significant hazards consideration determination:
As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

Criterion 1 - Does Not Involve a Significant Increase in the Probability or Consequences of an Accident Previously Evaluated.

The proposed changes do not affect reactor operations or accident analyses, have no radiological consequences, and are considered to be purely administrative in nature. All requirements relocated from the TSs have been evaluated with respect to the four criteria of the NRC "Final Policy Statement On Technical Specifications Improvements" as presented in SECY-93-067, and found to meet none of the criteria for inclusion in the TS.

Therefore, this change does not involve a significant increase in the probability or consequences of any accident previously evaluated.

Criterion 2 - Does Not Create the Possibility of a New or Different Kind of Accident from any Previously Evaluated.

The proposed changes introduce no new mode of plant operation and do not affect the operability of safety-related equipment. All requirements relocated or deleted from the TSs have been evaluated with respect to the four criteria of the NRC "Final Policy Statement On Technical Specifications Improvements" as presented in SECY-93-067, and found to meet none of the criteria for inclusion in the TS.

Therefore, this change does not create the possibility of a new or different kind of accident from any previously evaluated.

Criterion 3 - Does Not Involve a Significant Reduction in the Margin of Safety.

Existing TS operability and surveillance requirements are not reduced by the proposed change, thus no margins of safety are reduced. All requirements relocated or deleted from the TSs have been evaluated with respect to the four criteria of the NRC "Final Policy Statement On Technical Specifications Improvements" as presented in SECY-93-067, and found to meet none of the criteria for inclusion in the TS.

Therefore, this change does not involve a significant reduction in the margin of safety.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room
location: Tomlinson Library, Arkansas
Tech University, Russellville, Arkansas
72801

Attorney for licensee: Nicholas S. Reynolds, Esquire, Winston and Strawn,

1400 L Street, N.W., Washington, D.C.
20005-3502

NRC Project Director: William D.
Beckner

Entergy Operations Inc., Docket No. 50-
382, Waterford Steam Electric Station,
Unit 3, St. Charles Parish, Louisiana

Date of amendment request: February
9, 1993 as supplemented by letter dated
July 22, 1994

Description of amendment request:
The proposed amendment would revise
Section 3.0 and 4.0 of the Technical
Specifications (TSs) consistent with the
provision and intent of Generic Letter
(GL) 87-09 dated June 4, 1987.

Basis for proposed no significant
hazards consideration determination:
As required by 10 CFR 50.91(a), the
licensee has provided its analysis of the
issue of no significant hazards
consideration, which is presented
below:

TS 3.0.4 prevents entry into an operational
mode or other specified condition unless
Limiting Conditions for Operations (LCOs)
are met without reliance on Action
Requirements. The intent of this TS is to
ensure that a higher mode of operation is not
entered when equipment is inoperable or
when parameters exceed their specified
limits.

The proposed change clarifies TS 3.0.4
such that LCOs with Action Statements that
permit continued operation for an unlimited
period of time are exempt from the
restrictions of TS 3.0.4. This provision is
modified to require an additional plant safety
review prior to implementing additional
exceptions to 3.0.4 other than those currently
stated in the individual specifications. This
proposed change is consistent with existing
NRC regulatory requirements for LCOs.

The proposed change to TS 4.0.3
incorporates a 24-hour delay in
implementing the Action Statements due to
a missed surveillance requirement when the
Action Statements provide a restoration time
that is less than 24 hours. As reflected in GL
87-09, this change is justified in that it is
overly conservative to assume that systems or
components are immediately inoperable
when a surveillance requirement has not
been performed. The NRC concludes in
Generic Letter 87-09 that a 24-hour time limit
balances the risks associated with an
allowance for completing the surveillance
within this period against the risks associated
with the potential for a plant upset and
challenge to safety systems when the
alternative is a shutdown to comply with
Action Statements before the surveillance
can be completed. The NRC further states
that the potential for a plant upset and
challenge to safety systems is increased if
surveillances are performed during actions to
initiate a shutdown to comply with Action
Requirements.

TS 4.0.4 has been modified to note that its
provisions shall not prevent passage through
or to operational modes as required to
comply with Action Requirements. This

change is consistent with the intent of the
existing TS and represents a clarification.

No previously analyzed accident scenario
is changed by the proposed TS changes
described above. Initiating conditions and
assumptions remain as previously analyzed.

Therefore, the proposed changes will not
involve a significant increase in the
probability or consequences of any accident
previously evaluated.

The proposed change to TS 3.0.4 is
administrative in nature. Entry into an
operational mode or other specified
condition will be allowed for those
specifications not currently stating an
exception to 3.0.4 when 1) the applicable
LCOs Action Requirement permits continued
operation for an unlimited period of time and
2) the PORC (plant operations review
committee) has reviewed and approved the
exception.

The proposed change to TS 4.0.3 will allow
continued operation for an additional 24-
hours after discovery of a missed
surveillance. As reflected in GL 87-09,
missing a surveillance does not mean that a
component or system is inoperable. In most
cases, surveillances provide positive
verification of operability.

The proposed change to TS 4.0.4 will
alleviate conflict within the TS. The change
is necessary to allow the plant to proceed
through or to required operational modes to
comply with Action Statements even if
applicable Surveillance Requirements may
not have been performed.

These changes do not affect the operation
of the plant or the manner in which it is
operated.

Therefore, the proposed changes will not
create the possibility of a new or different
kind of accident from any accident
previously evaluated.

The proposed change to TS 3.0.4 is
administrative in nature and will have no
impact on any margin of safety.

The proposed change to TS 4.0.3 will allow
up to 24-hours to perform a missed
surveillance. In some cases this will
eliminate the need for a plant shutdown. As
reflected in GL 87-09, the overall effect is an
increase in plant safety by avoiding
unnecessary shutdowns and associated
system transients due to missed
surveillances.

The proposed change to TS 4.0.4 will
eliminate an internal conflict within the TS
and allow the plant to proceed through or to
required operational modes to comply with
Action Statements even if applicable
Surveillance Requirements for that mode
may not have been performed. The NRC staff
has previously evaluated these change in
Generic Letter 87-09 and determined that the
TS modifications will result in improved TS.

Therefore, the proposed change will not
involve a significant reduction in a margin of
safety.

The NRC staff has reviewed the
licensee's analysis and, based on this
review, it appears that the three
standards of 10 CFR 50.92(c) are
satisfied. Therefore, the NRC staff
proposes to determine that the
amendment request involves no
significant hazards consideration.

Local Public Document Room

location: University of New Orleans
Library, Louisiana Collection, Lakefront,
New Orleans, Louisiana 70122

Attorney for licensee: N.S. Reynolds,
Esq., Winston & Strawn 1400 L Street
N.W., Washington, D.C. 20005-3502

NRC Project Director: William D.
Beckner

Florida Power and Light Company, et
al., Docket No. 50-335, St. Lucie Plant,
Unit No. 1, St. Lucie County, Florida

Date of amendment request: July 28,
1994

Description of amendment request:
The amendment will revise Technical
Specifications (TS) 3/4.4.13 to
incorporate Low Temperature
Overpressure Protection (LTOP)
requirements similar to those
recommended by the NRC staff via
Generic Letter 90-06. The proposed
changes are in accordance with the
resolution of Generic Issue 94 for St.
Lucie Units 1 and 2.

Basis for proposed no significant
hazards consideration determination:
As required by 10 CFR 50.91(a), the
licensee has provided its analysis of the
issue of no significant hazards
consideration, which is presented
below:

Pursuant to 10 CFR 50.92, a determination
may be made that a proposed license
amendment involves no significant hazards
consideration if operation of the facility in
accordance with the proposed amendment
would not: (1) involve a significant increase
in the probability or consequences of an
accident previously evaluated; or (2) create
the possibility of a new or different kind of
accident from any accident previously
evaluated; or (3) involve a significant
reduction in a margin of safety. Each
standard is discussed as follows:

(1) Operation of the facility in accordance
with the proposed amendment would not
involve a significant increase in the
probability or consequences of an accident
previously evaluated.

The changes proposed for St. Lucie Unit 1
Technical Specifications (TS) 3/4.4.13 are
similar to those recommended by the NRC
staff via Generic Letter 90-06 for Low
Temperature Overpressure Protection (LTOP)
systems. On the basis of technical studies
performed for Generic Issue 94, the staff
concluded that LTOP system unavailability is
a contributor to the risk associated with
overpressure transients during the shutdown
modes of plant operation. Revisions to the
actions required and the time for completion
of such actions, in the event that one or more
Power Operated Relief Valves (PORV)
become inoperable, provide more rigor than
the existing specifications and are designed
to increase LTOP system availability. The
administrative restrictions do not change the
results of existing analyses performed to
evaluate postulated accidents but will
improve the availability of systems designed
to mitigate pressure transients that could

occur within the LTOP range. Therefore, operation of the facility in accordance with the proposed amendment will not involve a significant increase in the probability or consequences of an accident previously evaluated.

(2) Operation of the facility in accordance with the proposed amendment would not create the possibility of a new or different kind of accident from any accident previously evaluated.

The proposed amendment will not change the physical plant or the modes of operation defined in the facility license. The changes do not involve the addition of new equipment or the modification of existing equipment, nor do they alter the design of St. Lucie plant systems. Therefore, operation of the facility in accordance with the proposed amendment would not create the possibility of a new or different kind of accident from any accident previously evaluated.

(3) Operation of the facility in accordance with the proposed amendment would not involve a significant reduction in a margin of safety.

The proposed amendment provides additional administrative restrictions for the operation of LTOP equipment. The applicability of Limiting Conditions of Operation (LCO) involving the PORVs will be extended to include Operational MODE 6 when the head is on the reactor vessel, and the rigor of required actions and action completion times in the event that one or more PORVs become inoperable will be increased. Consequently, the risk of low temperature operations will be reduced and safety during the shutdown modes of operation will be enhanced. Therefore, operation of the facility in accordance with the proposed amendment would not involve a significant reduction in a margin of safety.

Based on the discussion presented above and on the supporting Evaluation of Proposed TS Changes, FPL has concluded that this proposed license amendment involves no significant hazards consideration.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room location: Indian River Junior College Library, 3209 Virginia Avenue, Fort Pierce, Florida 34954-9003

Attorney for licensee: Harold F. Reis, Esquire, Newman and Holtzinger, 1615 L Street, NW., Washington, DC 20036

NRC Project Director: Victor M. McCree (Acting)

Northeast Nuclear Energy Company, et al., Docket No. 50-336, Millstone Nuclear Power Station, Unit No. 2, New London County, Connecticut

Date of amendment request: July 1, 1994

Description of amendment request:

The proposed amendment to the Technical Specification (TS) would: 1. Modify the facility by providing an auctioneered power supply for the engineered safety feature actuation system (ESFAS) sensor cabinets; 2. Reinstate the 2-out-of-4 sump recirculation system (SRAS) logic; 3. Change Table 3.3 of the (Safety Feature Actuation System Instrumentation) by adding Manual main steam isolation (MSI) (Trip Buttons); by removing note (f) which describes the SRAS logic as a modified 2-out-of-4 logic; and by replacing Action Statement 4 with an Action Statement that allows operation with a second inoperable channel, provided both channels are placed in the bypassed condition. 4. Add to the TS new limiting conditions for operation and new surveillance requirements together with BASES (TS 3.3.2.2 and 4.3.2.2.1 and 4.3.2.2.2) for the ESFAS sensor cabinet power supply drawers.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

...The proposed changes do not involve an SHC [significant hazards consideration] because the changes would not:

1. Involve a significant increase in the probability or consequences of an accident previously analyzed.

SRAS Logic Modification
Implementation of the auctioneered power supply for the sensor cabinets will permit the reinstatement of the original 2-out-of-4 (six possible combinations) logic for SRAS initiation. The current logic only has four possible combinations. Changing the minimum number of SRAS channels required to be operable from four to three does not significantly reduce the available actuation combinations. Operation with one channel inoperable will still provide a 2-out-of-3 logic (three possible trip combinations). With the current SRAS logic, operation with one channel in bypass does not meet the single failure criterion for proper SRAS operation. Amendment No. 168 prevents that condition.

Allowing continued operation with three operable channels is consistent with the original Millstone Unit No. 2 Technical Specifications (prior to Amendment No. 168).

Note (f), which describes the current logic, will no longer apply after the auctioneering circuit is installed. This note is for information only and has no associated action or surveillance requirements. Therefore, removal of note (f) cannot affect either the probability or consequences of a postulated accident.

In addition to the change in the minimum number of channels required to be operable, Action statement 4 will be revised to allow a limited period of two hours when a second

channel may be placed in bypass for performance of surveillance testing. This is acceptable due to the installation of the auctioneering circuit and restoration of the full SRAS logic. Prior to the implementation of the short term modifications and Amendment No. 168, Action Statement 2 also applied to the SRAS. That Action Statement allows two hours of operation with two channels out of service. However, Action Statement 2 requires one of the two channels to be placed in the tripped position.

Postulating a LOCA [loss-of-coolant accident] and an additional failure, while in an action statement that specifies a maximum allowed outage time, is beyond the design basis of Millstone Unit No. 2. However, with one SRAS channel in bypass and one in the tripped position, an additional failure (such as the loss of a DC vital bus) following the onset of a LOCA could result in a false SRAS signal.

From an overall safety perspective, the potential consequences from a false SRAS at the onset of a LOCA are more severe than those from the failure to automatically generate an actuation signal. Proposed Action Statement 4 would require actuation of the remaining channel (following a LOCA and a loss of DC bus as a second failure) to initiate the SRAS. The existing operation procedures instruct the operator to ensure that the SRAS actuation occurs when the refueling water storage tank level decreases to a predetermined value. In the unlikely event that a LOCA occurred while a Action Statement 4 and no SRAS was generated at the appropriate time due to an additional failure which prevents one channel from tripping, the SRAS would be manually initiated by the operator.

The amount of time that Millstone Unit No. 2 would operate under Action Statement 4 (with two SRAS channels in bypass) is approximately 6 hours per month. This is based on the requirement to conduct monthly channel functional tests for the three operable channels. The probability of a LOCA occurring during these surveillance, while in Action Statement 4, with a subsequent failure of the remaining 2-out-of-2 SRAS logic, is very low.

Sensor Cabinet Auctioneering
The proposed new Technical Specification 3.3.2.2, which establishes the requirements for the ESFAS sensor cabinets power supply drawers, permits 48 hours to restore an inoperable sensor cabinet power supply drawer to operable status. A power supply drawer renders it inoperable, or if either its normal or backup power is not available.

Existing Technical Specification 3.8.2.1 contains an 8-hour action statement for restoring the power sources (VA-10, 20, 30, and 40) if they become inoperable. The proposed 48-hour action statement for the power supply drawers is appropriate since the sensor cabinet would remain functional if either normal or alternate power was not available. However, a LOCA and an additional failure while in the action statement could result in a false SRAS, since two channels would be supplied from a single DC power supply.

Prior to Amendment No. 168, operation with an inoperable power supply drawer

could continue indefinitely, provided the provisions of Technical Specification 3/4.3.2 were followed. Operation with a power supply inoperable for an indefinite period of time places all the signals associated with that sensor cabinet in the tripped condition. This creates a 1-out-of-4 tripped condition for SRAS. In this condition, the single failure required to be postulated could result in a false SRAS actuation.

This 48-hour action statement is consistent with other action statements for ESFAS such as Action Statement 1 of Table 3.3-3. Also, this is consistent with the current wording of Action Statement 4 which allows 48 hours to restore an inoperable channel to operable while operating with the modified 2-out-of-4 logic.

MSI Trip Button Addition

The manual trip buttons provide a mechanism for the control room operator to initiate an MSI trip. The proposed Technical Specification change will require that a plant shutdown be initiated if either channel is out of service for more than 48 hours, and establishes a requirement for surveillance testing every refueling outage. Including the trip buttons in the Technical Specifications and establishing operation and surveillance requirements ensures their operability commensurate with their safety significance.

Based on the above, the changes to Technical Specification 3/4.3 do not increase the probability or consequence of an accident previously evaluated.

2. Create the possibility of a new or different kind of accident from any previously analyzed.

SRAS Logic Modification

Changing the number of channels required to be operable from four to three is acceptable since the original 2-out-of-4 logic will be restored. This change only affects the number and combinations of actuation channels necessary to initiate a SRAS. There is no change to the source or types of initiators, nor is there a change to the automatic response resulting from a SRAS.

Note (f), which described the modified logic, will no longer apply after the auctioneering circuit is installed. This note is for information only and has no associated action or surveillance requirements. Therefore, removal of note (f) cannot create a new or different kind of accident.

New Action Statement 4 restores the ability to operate for an indefinite period of time with one channel in bypass and for a limited period of time while two channels are out of service. The change from the original action statement to require that both channels be in bypass will prevent a false SRAS in the unlikely (and beyond design basis) event of a LOCA with an additional failure of a DC bus while in an LCO [limiting condition for operation].

Sensor Cabinet Auctioneering

The addition of a Technical Specification for the sensor cabinet power supply drawers does not create a potential for a new or different kind of accident. This new specification implements more restrictive operating requirements for the sensor cabinets. These are necessary to ensure that the sensor cabinets are energized from their primary power supply. The new specification

does not affect the initiation of a SRAS signal nor the type of signal produced.

The auctioneering modification does bring two vital AC facilities together via isolation devices. This introduces a potential for a new type of failure mechanism. As described in Attachment 1, adequate isolation ensures that a failure on one side of an isolation transformer does not adversely degrade the other side.

MSI Trip Button Addition

The manual trip buttons provide a mechanism for the control room operator to initiate an MSI trip. The Technical Specification change will require that a plant shutdown be initiated if either manual trip channel is out of service for more than 48 hours, and establishes a requirement for surveillance testing every refueling outage. The trip buttons were installed during the 1992 outage. Establishing operability requirements and surveillance frequency cannot create a new or different kind of accident.

Therefore, the proposed changes do not create the possibility of a new or different kind of accident from any previously analyzed.

3. Involve a significant reduction in the margin of safety.

The net effect of the proposed modifications is to improve the reliability of the ESFAS and restore the design 2-out-of-4 logic for the SRAS. The proposed modifications improve the availability of the ESFAS, and do not affect the vital AC instrument panels.

The Technical Specification changes establish controls for the use of the SRAS with the restored logic configuration. The combination of the auctioneering of the power supplies, the restoration of the 2-out-of-4 logic, and the revised Technical Specifications restores the margin of safety and operational flexibility originally designed for the sensor cabinets.

Based on the above, there is no reduction in the margin of safety.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room

Location: Learning Resource Center, Three Rivers Community-Technical College, Thames Valley Campus, 574 New London Turnpike, Norwich, Connecticut 06360.

Attorney for licensee: Gerald Garfield, Esquire, Day, Berry & Howard, City Place, Hartford, Connecticut 06103-3499.

NRC Project Director: John F. Stolz

PECO Energy Company, Docket No. 50-353, Limerick Generating Station, Unit 2, Montgomery County, Pennsylvania

Date of amendment request: June 30, 1994

Description of amendment request:

This amendment would remove certain remote shutdown system control valves and primary containment isolation valves from Technical Specifications Tables 3.3.7.4-1 and 3.6.3-1 respectively, as a result of eliminating the steam condensing mode of the Residual Heat Removal system.

Basis for proposed no significant hazards consideration determination:

As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

1. The proposed Technical Specifications (TS) changes do not involve a significant increase in the probability or consequences of an accident previously evaluated.

These proposed changes will result in abandoning in place certain remote shutdown system control valves and removing from service and abandoning in place certain Primary Containment Isolation Valves (PCIVs) associated with the Residual Heat Removal (RHR) system steam condensing mode, and will remove the interface between the High Pressure Coolant Injection (HPCI) and RHR systems, therefore changing the primary containment pressure boundary.

The RHR system steam condensing mode is a non-safety related function of the RHR system; however, the pressure and structural integrity of the associated piping and valves are safety-related. These proposed changes will not affect any components required to perform the safety-related function of the RHR or HPCI systems.

The ability of the RHR or HPCI systems to respond to an accident will not be degraded. Only valves specifically dedicated for use for the RHR system steam condensing mode will be abandoned in-place, or removed from the plant. The valves' handswitches which are part of the remote shutdown panel (RSP) controls, will be physically removed from the RSP, since they will not perform any function (i.e., the associated valves will have the electrical power removed). The flanges and penetration caps that will become part of the primary containment boundary will be periodically tested for leakage as required by TS and 10CFR50, Appendix J. All piping and components that will remain operable will meet the original design requirements. The other modes of operation of the RHR system (e.g., Low Pressure Coolant Injection (LPCI), Shutdown [Cooling] (SDC)) will not be affected by these changes. Therefore, the proposed TS changes do not involve an increase in the probability or consequences of an accident previously evaluated.

2. The proposed TS changes do not create the possibility of a new or different kind of accident from any accident previously evaluated.

No new failure modes of RHR or HPCI systems are created by the proposed TS changes. The proposed changes will have no impact on the existing High Energy Line Break (HELB) analysis for Limerick Generating Station (LGS). All valves or

piping removed and/or abandoned in place, are dedicated specifically for the RHR system steam condensing mode, and will not affect the operation of any components or piping required for other modes of operation of the RHR or HPCI systems. Therefore, the proposed TS changes do not create the possibility of a new or different kind of accident from any previously evaluated.

3. The proposed TS changes do not involve a significant reduction in a margin of safety.

The steam condensing mode is a non-safety related function of the RHR system and, therefore, is not addressed in the TS. This mode will be physically separated from the other modes of operation of RHR and HPCI systems, and consequently, will not preclude them from performing their safety-related functions. The remote shutdown system control valves to be abandoned in place are not being used presently, and the proposed changes will not impact the safety operation of LGS Unit 2. The primary containment penetration caps, safety-related pipe caps and the flanges replacing the removed PCIVs will be designed, fabricated and installed in accordance with the original design requirements, i.e., American Society of Mechanical Engineers (ASME) Boiler and Pressure Vessel (B&PV) Code, Section III, 1971 Edition with Addenda through Winter 1971. The added penetration caps and flanges will be capable of maintaining the primary containment pressure boundary and isolation capabilities that were required of the PCIVs and will be tested for leakage periodically, as required by TS and 10 CFR 50, Appendix J. Additionally, all piping and components that will remain operable will meet original design requirements. Therefore, the proposed TS changes do not involve a reduction in a margin of safety.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room
location: Pottstown Public Library, 500 High Street, Pottstown, Pennsylvania 19464.

Attorney for licensee: J. W. Durham, Sr., Esquire, Sr. V. P. and General Counsel, PECO Energy Company, 2301 Market Street, Philadelphia, Pennsylvania 19101

NRC Project Director: Charles L. Miller

Pennsylvania Power and Light Company, Docket Nos. 50-387 and 50-388 Susquehanna Steam Electric Station, Units 1 and 2, Luzerne County, Pennsylvania

Date of amendment requests: July 19, 1994

Description of amendment request: This amendment will change the Technical Specification 3.1.5 for each unit for the standby liquid control

system (SLCS) to remove the operability requirement for the SLCS while in Operational Condition 5 (refueling) with any control rod withdrawn, and to delete the 18-month system surveillance requirement (Surveillance Requirement 4.1.5.d.3).

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

1. This proposal does not involve a significant increase in the probability or consequences of an accident previously evaluated.

The proposed Technical Specification change to delete the operability requirement for the SLC System in OPCON 5* (OPERATIONAL CONDITION 5 with any control rod withdrawn) does not affect the probability or consequences of an accident previously evaluated. Design basis accident mitigation scenarios for SSES in OPCON 5 do not depend on, or require, SLC operability; therefore, the proposed change to delete SLC operability in OPCON 5* does not affect the probability or consequences of an accident previously evaluated.

The proposed Technical Specification change to delete Surveillance Requirement 4.1.5.d.3, 18 month SLC heater operability check, does not affect the probability or consequences of an accident previously evaluated. Regarding the SLC heater function, the operability of the SLC system depends on maintaining the temperature of the sodium pentaborate solution above 70°F to prevent the boric acid from precipitating out of solution. SLC heater 'A' is used to maintain tank temperature between 85°F and 95°F, thus ensuring that the boric acid remains in solution. The operability of the heater 'A' is verified through the daily performance of Technical Specification Surveillance Requirement 4.1.5.a.1, which checks SLC solution temperature, and a control room alarm. Heater 'B' functions to raise SLC solution temperature prior to the mixing of SLC chemicals - the mixing of sodium pentaborate and water is an endothermic (heat consuming) reaction. The operability of heater 'B' is verified at the time when chemicals are added to the SLC tank, since a precondition for adding the chemicals is using heater 'B' to increase tank temperature to 100°F. Heater 'B' does not function to maintain tank temperature during normal operation. Therefore, the proposed change does not impact Susquehanna's ability to maintain SLC solution temperature and thus does not increase the probability or consequences of an accident previously evaluated.

2. This proposal does not create the possibility of a new or different kind of accident or [sic] from any accident previously evaluated.

The proposed Technical Specification change to delete the operability requirement for the SLC System in OPCON 5* does not create the possibility of a new or different kind of accident or [sic] from any accident

previously evaluated. The purpose of the SLC System is to provide backup capability for bringing the reactor from full power to a cold, Xenon-free shutdown, assuming that none of the withdrawn control rods can be inserted. This basis is consistent with the required operability of the SLC System in OPCONs 1 & 2. The proposed change does not affect the ability of SLC to meet its design basis. No credit is taken for SLC in OPCON 5 to mitigate the effects of reactivity transients, and the SLC system is not designed to terminate an inadvertent criticality event during core alterations (OPCON 5) with vessel water level at least 22 feet above top of vessel flange. Therefore, no new or different accident scenarios are created by the proposed change.

The proposed Technical Specification change to delete Surveillance Requirement 4.1.5.d.3, 18 month SLC heater operability check, does not create the possibility of a new or different kind of accident or [sic] from any accident previously evaluated. The proposed change does not affect systems, structures, or components (SSCs) or the operation of these [SSCs]. The heating and heater control subsystems of the SLC system will continue to function as they were designed. The proposed change does not alter the heating limits or the method for maintaining SLC solution temperature. Therefore, the proposed change does not create the possibility of a new or different kind of accident or [sic] from any accident previously evaluated. 3. This change does not involve a significant reduction in a margin of safety.

The proposed Technical Specification change to delete the operability requirement for the SLC System in OPCON 5* does not involve a significant reduction in a margin of safety. The potential for a decrease in the margin of safety, under this proposed change, would be associated with periods during OPCON 5* when the SLC system was not operable. Allowing the SLC system to be inoperable during OPCON 5* with the vessel level at least 22 feet above top of vessel flange, represents no reduction in the margin of safety since the SLC System is not designed to terminate an inadvertent criticality event with a greater volume of water in the reactor. Having the SLC system inoperable in OPCON 5* with reactor water levels at normal operating volumes, does not significantly reduce the margin of safety because of the number of other design and operating features which act to prevent inadvertent criticality events. Adequate shutdown margin is maintained through design and administrative controls; including, Shutdown Margin Demonstration, Technical Specification 3.1.1, defueling and refueling procedures, and refueling interlocks. In addition, the Reactor Protection System monitors for recriticality and actuates the Control Rod Scram function if a significant reactivity addition is sensed.

The proposed Technical Specification change to delete Surveillance Requirement 4.1.5.d.3, 18 month SLC heater operability check, does not involve a significant reduction in a margin of safety. Adequate controls are in place, independent of the 18 month heater operability check, to ensure

that the temperature of the sodium pentaborate solution is maintained above 70° F. These controls include Surveillance Requirement 4.1.5.a.1, which checks SLC solution temperature daily, a control room alarm on low and high temperature, and the ambient temperature conditions in the SLC area which prevent rapid changes in SLC solution temperature. Operability of the 'B' heater is not needed to maintain SLC solution temperature, and the operability of this heater is verified at the time when chemicals are added to the SLC tank.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room
location: Osterhout Free Library,
Reference Department, 71 South
Franklin Street, Wilkes-Barre,
Pennsylvania 18701

Attorney for licensee: Jay Silberg,
Esquire, Shaw, Pittman, Potts and
Trowbridge, 2300 N Street NW.,
Washington, DC 20037

NRC Project Director: Charles L.
Miller Power Authority of the State of
New York, Docket No. 50-333, James A.
FitzPatrick Nuclear Power Plant,
Oswego County, New York

Date of amendment request: June 13,
1994

Description of amendment request:
The proposed amendment would
modify the Facility Operating License
by removing License Condition 2.E.
This condition applies to the
construction cleanup, restoration, and
maintenance of transmission lines. It
is incorporated into the Facility Operating
License the requirements of U.S.
Department of Interior publication
"Environmental Criteria for Electric
Transmission Systems" - 1970. The
proposed amendment was requested to
eliminate duplication of regulatory
authority by government agencies of the
same activity.

**Basis for proposed no significant
hazards consideration determination:**
As required by 10 CFR 50.91(a), the
licensee has provided its analysis of the
issue of no significant hazards
consideration, which is presented
below:

Operation of the FitzPatrick plant in
accordance with the proposed Amendment
would not involve a significant hazards
consideration as defined in 10 CFR 50.92,
since it would not:

1. involve a significant increase in the
probability or consequences of an accident
previously evaluated.

The proposed change will remove a license
condition unrelated to nuclear safety. License
condition 2.E incorporated into the Operating

License the requirements of U.S. Department
of Interior publication "Environmental
Criteria for Electric Transmission Systems" -
1970. The goal of this standard is to
"safeguard aesthetic and environmental
values within the constraints imposed by the
current state of high-voltage transmission
technology." License condition 2.E addresses
the preservation of the environment and
natural resources. Removing this condition
from the Facility Operating License has no
bearing on plant safety or the health and
safety of the public considering its non-
nuclear safety nature. The transmission line
right-of-ways maintained by the Authority
are subject to regulation by other State and
Federal agencies. Removal of this license
condition will not affect operation of safety
related structures, systems or components
nor affect the quality assurance program at
the FitzPatrick plant. Therefore, the proposed
change does not involve a significant
increase in the probability or consequences
of an accident previously evaluated.

2. create the possibility of a new or
different kind of accident from any accident
previously evaluated.

License condition 2.E of the James A.
FitzPatrick Plant Operating License applies
to the construction cleanup, restoration, and
maintenance of transmission lines. The
Authority's transmission lines are managed
under guidelines based on the "Generic
Transmission Line Right-of-Way
Management" plan requirements. The
requirements imposed by the plan on the
FitzPatrick transmission line right-of-ways
exceed those of the U.S. Department of
Interior publication referenced in license
condition 2.E in both scope and details.
Therefore, implementing the proposed
change will not create the possibility of a
new or different kind of accident from any
accident previously evaluated.

3. involve a significant reduction in a
margin of safety.

License condition 2.E of the James A.
FitzPatrick Operating License applies to the
construction cleanup, restoration, and
maintenance of transmission lines. The
requirements imposed by this license
condition are unrelated to nuclear safety.
Continued operation of the plant without
Condition 2.E does not involve a significant
reduction in any margin of safety.

The NRC staff has reviewed the
licensee's analysis and, based on this
review, it appears that the three
standards of 50.92(c) are satisfied.
Therefore, the NRC staff proposes to
determine that the amendment request
involves no significant hazards
consideration.

Local Public Document Room
location: Reference and Documents
Department, Penfield Library, State
University of New York, Oswego, New
York 13126.

Attorney for licensee: Mr. Charles M.
Pratt, 1633 Broadway, New York, New
York 10019.

NRC Project Director: Michael L.
Boyle

**Power Authority of the State of New
York, Docket No. 50-333, James A.
FitzPatrick Nuclear Power Plant,
Oswego County, New York**

Date of amendment request: July 21,
1994

Description of amendment request:
The proposed changes would modify
paragraph 2.C.(3) of the Facility
Operating License and relocate fire
protection requirements from the
Technical Specifications to an
administrative procedure. These
changes are based on the guidance
contained in NRC Generic Letter 86-10,
"Implementation of Fire Protection
Requirements," and Generic Letter 88-
12, "Removal of Fire Protection
Requirements from Technical
Specifications."

**Basis for proposed no significant
hazards consideration determination:**
As required by 10 CFR 50.91(a), the
licensee has provided its analysis of the
issue of no significant hazards
consideration, which is presented
below:

Operation of the FitzPatrick plant in
accordance with the proposed Amendment
will not involve a significant hazards
consideration as defined in 10 CFR 50.92,
because:

(1) This change does not involve a
significant increase in the probability or
consequences of an accident previously
evaluated because no modifications, no
changes to operating procedure requirements,
no reduction in administrative controls and
no reduction in equipment reliability are
being made as a result of these changes. This
proposed amendment relocates the fire
protection LCOs [Limiting Conditions for
Operation] and Surveillance Requirements
from the Technical Specifications to an
Administrative Procedure. No significant
changes in content are being made to the
Technical Specification requirements that are
being relocated. Operating limitations will
continue to be in effect, and required
surveillances will continue to be performed
in accordance with written procedures and
instructions auditable by the NRC.

Although future proposed changes to the
fire protection program elements previously
located in the Technical Specifications will
no longer be controlled by 10 CFR 50.36,
proposed changes to the Fire Protection
requirements will be controlled by the
License Condition and plant procedures.
Programmatic controls will continue to
assure that fire protection program changes
do not reduce the effectiveness of the
program to achieve and maintain safe
shutdown in the event of a fire.

(2) The possibility of an accident or
malfunction of a different type than
evaluated previously in the safety analysis
report is not created because no reduction to
the fire protection requirements, no
modifications, no changes to operating
procedure requirements, no reduction in
administrative controls and no reduction in
equipment reliability are being made as a

result of these changes. Programmatic controls will continue to assure that fire protection program changes do not reduce the effectiveness of the program to achieve and maintain safe shutdown in the event of a fire.

(3) This proposed amendment does not involve a reduction to the approved fire protection program or Fire Protection Technical Specification requirements because the Technical Specification fire protection requirements are being relocated, with no significant change in content, to an administrative procedure. Since there is no reduction in the requirements, no modifications, no changes to operating procedure requirements, no reduction in administrative controls and no reduction in equipment reliability are being made as a result of these changes, there is no reduction in the margin of safety.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room location: Reference and Documents Department, Penfield Library, State University of New York, Oswego, New York 13126.

Attorney for licensee: Mr. Charles M. Pratt, 1633 Broadway, New York, New York 10019.

NRC Project Director: Pao Tsin Kuo

Power Authority of The State of New York, Docket No. 50-286, Indian Point Nuclear Generating Unit No. 3, Westchester County, New York

Date of amendment request: July 25, 1994

Description of amendment request: The licensee has requested an amendment to the Technical Specifications (TS) to revise Table 3.6-1 (Non-Automatic Containment Isolation Valves Open Continuously or Intermittently for Plant Operation) and Table 4.4-1 (Containment Isolation Valves) to delete valves SI-1833A(B) and add valves SI-MOV-1835A(B). The valves being deleted no longer perform a containment isolation function as a result of a modification which removed the boron injection tank. The valves being added are needed for testing the safety injection pumps.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

Consistent with the criteria of 10 CFR 50.92, the enclosed application is judged to involve no significant hazards based on the following information:

(1) Does the proposed license amendment involve a significant increase in the probability or consequences of any accident previously evaluated?

Response:

The proposed license amendment does not involve a significant increase in the probability or consequences of any accident previously evaluated. The change permits the removal of the two containment isolation valves on the Boron Injection Tank (BIT) bypass line. A previous amendment [Amendment No. 139, issued on October 15, 1993] to the Operating License removed the functional requirement for the BIT. Consequently, the function of the BIT bypass line to provide a Safety Injection (SI) pump test flow path has been rendered obsolete, permitting removal of the bypass line and associated valves. The bypass line will be cut and capped to assure containment integrity, therefore eliminating the need for containment isolation valves SI-1833A and SI-1833B. Opening the BIT outlet valve [SI-MOV-1835A or B] permits operability testing of the SI pumps, and is consistent with the current provision permitting opening of the BIT bypass valves. The changes do not impact the current operability and surveillance requirements for the Safety Injection System.

(2) Does the proposed license amendment create the possibility of a new or different kind of accident from any previously evaluated?

Response:

The proposed license amendment does not create the possibility of a new or different kind of accident from any previously evaluated. The change proposes to eliminate two containment isolation valves on the BIT bypass line whose function has been rendered obsolete by a previous amendment to the Operating License. The bypass line will be cut and capped to assure containment integrity, therefore eliminating the need for these containment isolation valves. Intermittent opening of the BIT outlet valve is consistent with the current provision permitting opening of the BIT bypass valves, thereby allowing operability testing of the SI pumps. The changes do not impact the operability or surveillance requirements for the Safety Injection System.

(3) Does the proposed amendment involve a significant reduction in a margin of safety?

Response:

The proposed license amendment does not involve a significant reduction in a margin of safety for the following reasons. Currently, an orientation deficiency with the inboard BIT bypass isolation valve exposes its stem packing to the non-isolable side of the valve. The modification corrects this problem by removing both isolation valves and capping the pipes to assure integrity of the Containment and Safety Injection System. Additionally, removal of the isolation valves removes the potential for containment leakage resulting from valve degradation. Finally, removal of the BIT bypass line and its associated isolation valves does not inhibit the ability to test the SI pumps since a previous modification approved in an Amendment to the Operating License removed the functional requirement for the

BIT. Consequently, the SI pumps may be flow tested with the BIT in service, rendering obsolete the function of the BIT bypass line. Intermittent opening of the BIT outlet valve is consistent with the current provision permitting opening of the BIT bypass valves, thereby allowing operability testing of the SI pumps.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10601.

Attorney for licensee: Mr. Charles M. Pratt, 10 Columbus Circle, New York, New York 10019.

NRC Project Director: Pao Tsin Kuo

Public Service Electric & Gas Company, Docket Nos. 50-272 and 50-311, Salem Nuclear Generating Station, Unit Nos. 1 and 2, Salem County, New Jersey

Date of amendment request: June 29, 1994

Description of amendment request: These proposed amendments would revise the Technical Specifications to increase the minimum volume of oil contained in the Diesel Fuel Oil Storage Tanks (DFOSTs) at the Salem Generating Station (SGS). It would also revise the Updated Final Safety Analysis Report (UFSAR) description of the fuel oil storage system capability.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

(1) [This proposal does] not involve a significant increase in the probability or consequences of an accident previously evaluated.

Emergency Diesel Generator (EDG) fuel oil is used to support mitigation of design basis events involving loss of the preferred (offsite) source of A.C. power. Fuel oil storage capacity has no effect on the probability of any accident previously evaluated.

Onsite fuel oil storage capability is designed to provide assurance of long term diesel operation to mitigate the consequences of a design basis accident. The proposed change would increase the minimum required volume in the Seismic Class I Diesel Fuel Oil Storage Tanks (DFOSTs), and would revise the Updated Final Safety Analysis Report (UFSAR), as part of an effort to reconstitute the basis for SGS fuel oil storage capacity. The DFOST inventory at the proposed minimum Technical Specification (TS) limit, combined with the emergency fill connection and Seismic Class III Fuel Oil

Storage Tank and transfer capability, would continue to provide a long term onsite fuel oil supply to the EDGs. Operations and Emergency Preparedness procedures would facilitate the transfer of fuel oil, and procurement from offsite sources as a contingency measure. Therefore, the ability to provide a long term supply of fuel oil to the EDG's is maintained, and the proposed change would not result in any significant increase in consequences of an accident previously evaluated.

(2) [This proposal does] not create the possibility of a new or different kind of accident from any accident previously evaluated.

The proposed change would increase the minimum DFOST level required by TS, and redefines the fuel oil storage and transfer systems' capability based on plant specific fuel oil consumption rate and EDG load profiles. These changes would not result in operation in any configuration prohibited by the present TS, and do not introduce the possibility of any new type of accident.

(3) [This change does] not involve a significant reduction in a margin of safety.

The EDG fuel oil storage and transfer capability would continue to support reliable, long term EDG operation, thereby maintaining an acceptable margin of safety relative to the ability of onsite A.C. power to support operation of equipment important to safety. The proposed changes do not involve a significant reduction in margin of safety.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room
location: Salem Free Public library, 112 West Broadway, Salem, New Jersey 08079

Attorney for licensee: Mark J. Wetterhahn, Esquire, Winston and Strawn, 1400 L Street, NW., Washington, DC 20005-3502

NRC Project Director: Charles L. Miller

Tennessee Valley Authority, Docket Nos. 50-259 and 50-296, Browns Ferry Nuclear Plant, Units 1 and 3, Limestone County, Alabama

Date of amendment request: March 31, 1994 (TS 319)

Description of amendment request: The proposed amendment revises the setpoints for instrumentation used to isolate high energy line breaks in the high pressure coolant injection (HPCI) and reactor core isolation cooling (RCIC) systems. The proposed amendment also defines specific areas where steam line space temperatures are monitored.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the

licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

1. The proposed amendment does not involve a significant increase in the probability or consequences of an accident previously evaluated.

The proposed changes to the HPCI and RCIC steam line space isolation setpoints do not affect any precursor for any design basis events or operational transients analyzed in the Browns Ferry Final Safety Analysis Report. Therefore, the probability of an accident previously evaluated is not increased.

The HPCI and RCIC steam line space high temperature isolations are provided to ensure automatic closure of each system's primary containment isolation valves for a HPCI or RCIC steam line break. The isolation occurs when a very small leak has occurred. If the small leak is allowed to continue without isolation, offsite dose limits may be reached. As a result of the environmental qualification program, the environmental responses of the reactor building to high energy line breaks were analyzed. TVA used computer modeling techniques to predict the temperature response of various reactor building zones to high energy line breaks. The results indicate that the setpoints for the HPCI and RCIC temperatures switches should be lowered. The lower setpoints assure the timely initiation of a closure signal to the primary containment isolation valves. Therefore, assuring the maximum allowable temperatures are not exceeded.

The proposed change to the HPCI and RCIC steam line space isolation setpoints are in the conservative direction and provides the same or earlier detection and isolation of HPCI and RCIC steam line breaks.

The proposed trip level settings are high enough to ensure that spurious trips do not occur from normal or transient system operation and low enough to ensure that line breaks are detected and isolated before design conditions are exceeded. Therefore, the proposed changes will not significantly increase the consequences of an accident previously evaluated.

2. The proposed amendment does not create the possibility of a new or different kind of accident from any accident previously evaluated.

The proposed change to the HPCI/RCIC steam line space high temperature isolations does not involve any modification to plant equipment or changes in operating procedures. No new failure modes are introduced. There is no effect on the function or operation of any other plant system. No new system interactions have been introduced by the change. The results of a break in the HPCI or RCIC steam lines remain as before. The HPCI or RCIC steam line area temperature switches will still detect a break due to an increase in area temperature and provide an initiation signal to close the system primary containment isolation valves to prevent reactor coolant loss. The proposed change will conservatively serve to detect and mitigate HPCI and RCIC line breaks more expeditiously.

Therefore, the proposed changes do not create the possibility of a new or different kind of accident.

3. The proposed amendment does not involve a significant reduction in a margin of safety.

The proposed change will not reduce the margin of safety. The proposed change ensure that HPCI and RCIC steam line breaks are isolated at the same or lower steam line area temperatures. Computer modeling techniques were utilized to predict the temperature response in various areas through which the HPCI and RCIC steam lines pass. The revised setpoints are established above the maximum expected normal room temperatures to avoid spurious actions due to ambient conditions and below the analytical limits to ensure timely pipe break detection and isolation. Substantial margin exist between the maximum temperature expected in each area and the minimum actuation temperature determined for each temperature switch. With the substantial margin between maximum temperatures for the areas and the minimum actuation temperature of the switches, the maximum temperatures cannot result in actuation of the switches. The design and function of the affected components has not been changed. Therefore, the proposed change does not involve a significant reduction in a margin of safety.

The NRC has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room
location: Athens Public Library, South Street, Athens, Alabama 35611

Attorney for licensee: General Counsel, Tennessee Valley Authority, 400 West Summit Hill Drive, ET 11H, Knoxville, Tennessee 37902

NRC Project Director: Mr. Frederick J. Hebbon

Tennessee Valley Authority, Docket No. 50-260, Browns Ferry Nuclear Plant, Unit 2, Limestone County, Alabama

Date of amendment request: May 11, 1994 (TS 347T)

Description of amendment request: The proposed amendment extends the allowed outage time for the Browns Ferry Nuclear Plant (BFN) Unit 2 250 volt DC (direct current) control power supplies from 5 to 45 days. The amendment is a temporary revision to the BFN Unit 2 Technical Specifications (TS) to permit replacement of batteries and other hardware.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration, which is presented below:

1. The proposed amendment does not involve a significant increase in the probability or consequences of an accident previously evaluated.

The proposed change involves temporarily (one-year period) extending the 5-day AOT [allowed outage time] for the 250-volt shutdown board control power supplies to 45 days. As such, this change does not increase the probability of any accident previously analyzed.

The 250-volt DC Power System is required to function to mitigate the consequences of design basis accidents. The loss of a single 250-volt DC shutdown board control power supply will result in a loss of control power for the 480-volt and the 4160-volt shutdown board that it serves. Loss of control power results in loss of only those engineered safeguards supplied by its respective shutdown boards. Redundant safe shutdown equipment exists to mitigate the consequences of design basis accidents. As discussed in Final Safety Analysis Report (FSAR) subsection 8.6.4.3, a single failure of a shutdown board control power supply is acceptable.

Loss of a single 250-volt plant DC power supply will not prevent Unit 2 safe shutdown. The 250-volt plant DC power supply system is designed so that any two out of the three power supplies carry the entire load needed for safe shutdown. As discussed in FSAR subsection 8.6.4.2 a single failure of a 250-volt plant DC power supply is acceptable.

At no time will control power be unavailable to the shutdown boards during the system upgrades. The proposed change will only increase the time allowed to operate the plant while a 250-volt DC shutdown board control power supply is out of service.

The proposed TS change allows an additional 40 days to perform system upgrades and results in a small increase in risk. This small increase in risk is associated with the probability and consequences of a 250-volt plant DC power supply malfunction while it is supplying shutdown board control power. The increase in risk associated with extending the AOT was analyzed in a Probabilistic Safety Assessment (PSA) and determined to be approximately 0.3 percent. This small increase in risk is determined to be insignificant and well within the uncertainty bounds of the PSA.

The proposed TS change does not change the function of any plant structure, system or component. The proposed change allows for improvements to the 250-volt DC shutdown board control power supply system. The improvements will increase the capability and reliability of the system. Qualified backup power will be utilized at all times during system modifications. Only one power supply will be out of service at a time during the modifications.

The small increase in risk is more than offset by the increased capability, capacity, and reliability of the new power supplies. Therefore, the power supply modifications will result in a net overall safety benefit.

[The licensee has also committed to implement compensatory measures while performing the power supply modifications.

These measures provide additional confidence that potential accident consequences are not increased.]

2. The proposed amendment does not create the possibility of a new or different kind of accident from any accident previously evaluated.

Extending the 5-day AOT for the 250-volt shutdown board control power supplies to 45 days does not create the possibility of a new or different kind of accident, nor does it increase the probability that an accident will occur. The AOT extension does not involve plant modifications that could create the possibility of a new or different kind of accident from any of those discussed in the FSAR.

The 250-volt DC shutdown board control power supply modifications involve replacement of the existing components with more reliable, increased capacity equipment having the same functions as before.

3. The proposed amendment does not involve a significant reduction in a margin of safety.

The proposed TS change involves a risk increase of approximately 0.3 percent. TVA [the Tennessee Valley Authority, the licensee] considers this small increase to be insignificant. TVA also considers that the small increase in risk is offset by the benefits associated with replacing the control power supplies with new, upgraded equipment. Therefore, the proposed TS change does not involve a significant reduction in a margin of safety.

[The licensee has also committed to implement compensatory measures while performing the power supply modifications. These measures provide additional capability to mitigate an accident, minimizing any effect on safety margin.]

The NRC has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room location: Athens Public Library, South Street, Athens, Alabama 35611

Attorney for licensee: General Counsel, Tennessee Valley Authority, 400 West Summit Hill Drive, ET 11H, Knoxville, Tennessee 37902

NRC Project Director: Mr. Frederick J. Hebdon

Wisconsin Electric Power Company, Docket Nos. 50-266 and 50-301, Point Beach Nuclear Plant, Unit Nos. 1 and 2, Town of Two Creeks, Manitowoc County, Wisconsin

Date of amendment request: July 18, 1994

Description of amendment request:

The proposed amendment would modify Point Beach Nuclear Plant Technical Specification (TS) 15.3.7, "Auxiliary Electrical Systems," by including an allowed outage time for one of the four connected station battery

chargers and subsequent shutdown requirements. The basis for Section 15.3.7 would also be revised to support the above changes.

Basis for proposed no significant hazards consideration determination: As required by 10 CFR 50.91(a), the licensee has provided its analysis of the issue of no significant hazards consideration which is presented below:

In accordance with the requirements of 10 CFR 50.91(a), Wisconsin Electric Power Company (Licensee) has evaluated the proposed changes against the standards of 10 CFR 50.92 and has determined that the operation of Point Beach Nuclear Plant, Units 1 and 2, in accordance with the proposed amendments, does not present a significant hazards consideration. A proposed facility operating license amendment does not present a significant hazards consideration if operation of the facility in accordance with the proposed amendment will not:

1. Create a significant increase in the probability or consequences of an accident previously evaluated; or
2. Create the possibility of a new or different kind of accident from any accident previously evaluated; or
3. Will not create a significant reduction in a margin of safety.

The proposed amendment allows operation for up to two hours with one out of the four connected station battery chargers out of service. The 2-hour outage time is based on Regulatory Guide 1.93 and reflects a reasonable time to assess plant status and either connect an operable battery charger to the affected DC bus or prepare to effect an orderly and safe shutdown of the operating unit(s). Since the batteries, chargers, and their associated vital instrument buses provide sufficient redundancy to assure the initiation of proper protective actions during degraded system conditions, operation of PBNP in accordance with these proposed amendments cannot create an increase in the probability or consequences of an accident previously evaluated, create a new or different kind of accident, or result in a significant reduction in a margin of safety. Therefore, the proposed changes do not present a significant hazards consideration.

The NRC staff has reviewed the licensee's analysis and, based on this review, it appears that the three standards of 10 CFR 50.92(c) are satisfied. Therefore, the NRC staff proposes to determine that the amendment request involves no significant hazards consideration.

Local Public Document Room location: Joseph P. Mann Library, 1516 Sixteenth Street, Two Rivers, Wisconsin 54241.

Attorney for licensee: Gerald Charnoff, Esq., Shaw, Pittman, Potts, and Trowbridge, 2300 N Street, NW., Washington, DC 20037.

NRC Project Director: John N. Hannon

Previously Published Notices Of Consideration Of Issuance Of Amendments To Facility Operating Licenses, Proposed No Significant Hazards Consideration Determination, And Opportunity For A Hearing

The following notices were previously published as separate individual notices. The notice content was the same as above. They were published as individual notices either because time did not allow the Commission to wait for this biweekly notice or because the action involved exigent circumstances. They are repeated here because the biweekly notice lists all amendments issued or proposed to be issued involving no significant hazards consideration.

For details, see the individual notice in the *Federal Register* on the day and page cited. This notice does not extend the notice period of the original notice.

Georgia Power Company, Docket No. 50-366, Edwin I. Hatch Nuclear Plant, Unit 2, Appling County, Georgia

Date of amendment request: July 19, 1994

Description of amendment request: The proposed amendment would revise Technical Specification 3.3.6.6 to permit the traversing incore probe (TIP) system to be considered operable with less than four operable TIP units. *Date of publication of individual notice in Federal Register:* July 22, 1994 (59 FR 37516) *Expiration date of individual notice:* Comment Period expires August 8, 1994; *Notice period expires:* August 22, 1994

Local Public Document Room location: Appling County Public Library, 301 City Hall Drive, Baxley, Georgia 31513

Notice Of Issuance Of Amendments To Facility Operating Licenses

During the period since publication of the last biweekly notice, the Commission has issued the following amendments. The Commission has determined for each of these amendments that the application complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendment.

Notice of Consideration of Issuance of Amendment to Facility Operating License, Proposed No Significant Hazards Consideration Determination, and Opportunity for A Hearing in

connection with these actions was published in the *Federal Register* as indicated.

Unless otherwise indicated, the Commission has determined that these amendments satisfy the criteria for categorical exclusion in accordance with 10 CFR 51.22. Therefore, pursuant to 10 CFR 51.22(b), no environmental impact statement or environmental assessment need be prepared for these amendments. If the Commission has prepared an environmental assessment under the special circumstances provision in 10 CFR 51.12(b) and has made a determination based on that assessment, it is so indicated.

For further details with respect to the action see (1) the applications for amendment, (2) the amendment, and (3) the Commission's related letter, Safety Evaluation and/or Environmental Assessment as indicated. All of these items are available for public inspection at the Commission's Public Document Room, the Gelman Building, 2120 L Street, NW., Washington, DC 20555, and at the local public document rooms for the particular facilities involved.

Carolina Power & Light Company, Docket No. 50-261, H. B. Robinson Steam Electric Plant, Unit No. 2, Darlington County, South Carolina

Date of application for amendment: September 15, 1993

Brief description of amendment: The amendment revises the pressure-temperature limits from 15 to 24 effective full power years.

Date of issuance: July 29, 1994

Effective date: July 29, 1994

Amendment No. 149

Facility Operating License No. DPR-23. Amendment revises the Technical Specifications.

Date of initial notice in Federal Register: October 13, 1993 (58 FR 52980) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 29, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Hartsville Memorial Library, Home and Fifth Avenues, Hartsville, South Carolina 29550

Carolina Power & Light Company, et al., Docket No. 50-400, Shearon Harris Nuclear Power Plant, Unit 1, Wake and Chatham Counties, North Carolina

Date of application for amendment: February 4, 1994

Brief description of amendment: The amendment revises the Action Statement of TS 3.6.5, Vacuum Relief System, to require in Modes 1-4 with one vacuum relief system inoperable

that the system be restored to the operable status within seventy-two hours or be in at least hot standby within the next six hours.

Date of issuance: July 27, 1994

Effective date: July 27, 1994

Amendment No. 49

Facility Operating License No. NPF-63. Amendment revises the Technical Specifications.

Date of initial notice in Federal Register: March 30, 1994 (59 FR 14886) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 27, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Cameron Village Regional Library, 1930 Clark Avenue, Raleigh, North Carolina 27605.

Carolina Power & Light Company, et al., Docket No. 50-400, Shearon Harris Nuclear Power Plant, Unit 1, Wake and Chatham Counties, North Carolina

Date of application for amendment: May 11, 1994

Brief description of amendment: The amendment revises TS 3.4.2.3 to establish limits on reactor power level as a function of total reactor coolant system (RCS) flow rate up to 5 percent below the current specified flow rate.

Date of issuance: July 27, 1994

Effective date: July 27, 1994

Amendment No. 50

Facility Operating License No. NPF-63. Amendment revises the Technical Specifications.

Date of initial notice in Federal Register: May 25, 1994 (59 FR 27079) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 27, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Cameron Village Regional Library, 1930 Clark Avenue, Raleigh, North Carolina 27605.

Commonwealth Edison Company, Docket Nos. STN 50-456 and STN 50-457, Braidwood Station, Unit Nos. 1 and 2, Will County, Illinois

Date of application for amendments: March 30, 1994, as supplemented by letters dated June 13, June 14, July 11, July 21 and July 28, 1994

Brief description of amendments: The amendment revises the Technical Specifications (TSs) by changing the Unit 1 heatup and cooldown pressure-temperature (P-T) curves [i.e., Figures 3.4-2a and 3.4-3a] to incorporate a newly determined reactor pressure vessel (RPV) reference nil-ductility temperature, RT_{NDT}. This new value of

RT_{NDT} was determined from the licensee's analysis of the first irradiation sample removed from Unit 1. The setpoint curve contained in Figure 3.4-4a for the Unit 1 Low Temperature Overpressure Protection System (LTOPS) is also revised to reflect the changes in the P-T curves and to provide a margin for uncertainties in measuring the reactor pressure. Additionally, the amendment updates the removal schedule of RPV surveillance capsules for both units in accordance with the American Society for Testing Materials (ASTM) Standard ASTM E185-82. Finally, the amendment incorporates an editorial change for Unit 2 in which some clarifying text was added in the Table of Contents to indicate the lifetime applicability of Figure 3.4-4b for Unit 2.

Date of issuance: July 29, 1994

Effective date: July 29, 1994

Amendment Nos.: 53 and 53

Facility Operating License Nos. NPF-72 and NPF-77. The amendments revised the Technical Specifications.

Date of initial notice in Federal Register: May 12, 1994 (59 FR 24747) The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated July 29, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Wilmington Township Public Library, 201 S. Kankakee Street, Wilmington, Illinois 60481.

Commonwealth Edison Company, Docket Nos. 50-373 and 50-374, LaSalle County Station, Units 1 and 2, LaSalle County, Illinois

Date of application for amendments: September 10, 1993 as supplemented November 17, 1993

Brief description of amendments: The amendments revise the LaSalle County Station, Units 1 and 2 Updated Final Safety Analysis Report Section 11.5.2.1.4 to specify that operator action is required to trip the mechanical vacuum pump upon receipt of a main steam line high radiation alarm, rather than the action of an automatic trip, which is currently described in the UFSAR. NRC approval was required because the required operator action, an existing condition, is contrary to that described in the UFSAR and the NRC's Safety Evaluation Report related to the operation of LaSalle County station (NUREG-0519), and involved an unreviewed safety question.

Date of issuance: July 26, 1994

Effective date: July 26, 1994

Amendment Nos.: 101 and 85

Facility Operating License Nos. NPF-11 and NPF-18. The amendments revised the UFSAR.

Date of initial notice in Federal Register: December 1, 1993 (58 FR 63403) The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated July 26, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Public Library of Illinois Valley Community College, Rural Route No. 1, Oglesby, Illinois 61348.

Commonwealth Edison Company, Docket Nos. 50-295 and 50-304, Zion Nuclear Power Station, Units 1 and 2, Lake County, Illinois

Date of application for amendments: June 16, 1994

Brief description of amendments: The amendments change specification 3/4.10.1 to recognize the exemption of a single valve on each unit from Type C testing until the next refueling outage on each unit.

Date of issuance: August 1, 1994

Effective date: August 1, 1994

Amendment Nos.: 155 and 143

Facility Operating License Nos. DPR-39 and DPR-48. The amendments revised the Technical Specifications.

Date of initial notice in Federal Register: June 30, 1994 (59 FR 33798) Public comments requested as to proposed no significant hazards consideration: yes. The notice provided an opportunity to submit comments on the Commission's proposed no significant hazards consideration determination. No comments have been received. The notice also provided an opportunity to request a hearing by August 1, 1994, but indicated that if the Commission makes a final no significant hazards consideration determination, any such hearing would take place after issuance of the amendment. The Commission's related evaluation of the amendment and final significant hazards consideration determination is contained in a Safety Evaluation dated August 1, 1994.

Local Public Document Room location: Waukegan Public Library, 128 N. County Street, Waukegan, Illinois 60085.

Consolidated Edison Company of New York, Docket No. 50-003 and Docket No. 50-247, Indian Point Nuclear Generating Unit Nos. 1 and 2, Westchester County, New York

Date of application for amendments: September 29, 1993

Brief description of amendments: The amendments revise the Technical Specifications (TSs) to change the

submittal frequency of the Radioactive Effluent Release Report from semiannually to annually, and change the reporting date.

Date of issuance: July 21, 1994

Effective date: As of the date of issuance to be implemented within 30 days.

Amendment Nos.: 44 and 172

Facility Operating License Nos. DPR-5 and DPR-26: Amendments revised the Technical Specifications.

Date of initial notice in Federal Register: November 24, 1993 (58 FR 62153) The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated July 21, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610.

Consolidated Edison Company of New York, Docket No. 50-247, Indian Point Nuclear Generating Unit No. 2, Westchester County, New York

Date of application for amendment: September 29, 1993, as supplemented by letter dated April 1, 1994.

Brief description of amendment: The amendment revises the Technical Specifications to remove the cycle-specific parameter limits and to reference a Core Operating Limits Report containing these limits. These changes are in accordance with the guidance provided in Generic Letter 88-16, "Removal of Cycle-Specific Parameter Limits from Technical Specifications."

Date of issuance: July 26, 1994

Effective date: This license amendment is effective as of the date of issuance of the COLR by the licensee to be implemented no later than the return to operation following the 1995 refueling outage.

Amendment No.: 173

Facility Operating License No. DPR-26: Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: November 24, 1993 (58 FR 62154) The April 1, 1994, provided additional information that did not change the initial determination. The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 26, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610. Consolidated Edison Company of New York, Docket No. 50-247, Indian Point Nuclear Generating

Unit No. 2, Westchester County, New York

Date of application for amendment: January 28, 1994

Brief description of amendment: The amendment revises the TSs to change the containment isolation valve testing frequency and the acceptance criteria for the combined containment leakage rate to accommodate operation on a 24-month fuel cycle. These changes follow the guidance provided in Generic Letter 91-04, "Changes in Technical Specification Surveillance Intervals to Accommodate a 24-Month Fuel Cycle."

Date of issuance: July 29, 1994

Effective date: As of the date of issuance to be implemented within 30 days.

Amendment No.: 174

Facility Operating License No. DPR-26: Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: April 13, 1994 (59 FR 17596) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 29, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610.

Consumers Power Company, Docket No. 50-155, Big Rock Point Plant, Charlevoix County, Michigan

Date of application for amendment: April 22, 1994, as supplemented July 6, 1994

Brief description of amendment: The amendment revised the reactor vessel pressure-temperature limits in the Technical Specifications. The change insures that the vessel fracture toughness requirements of Section V of 10 CFR Part 50, Appendix G, are satisfied through end of life.

Date of issuance: July 25, 1994

Effective date: July 25, 1994

Amendment No.: 113

Facility Operating License No. DPR-6: Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: May 12, 1994 (59 FR 24749). The July 6, 1994, letter provided clarifying information within the scope of the initial notice and did not affect the staff's proposed no significant hazards consideration findings. The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 25, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: North Central Michigan

College, 1515 Howard Street, Petoskey, Michigan 49770.

Detroit Edison Company, Docket No. 50-341, Fermi-2, Monroe County, Michigan

Date of application for amendment: May 10, 1994

Brief description of amendment: The amendment revises the Fermi-2 Technical Specifications (TS) to remove Table 3.6.3-1, the list of primary containment isolation valves and Table 3.8.4.3-1, the list of safety systems' motor-operated valve thermal overload protection from the TS to administrative procedures in accordance with the guidance contained in Generic Letter 91-08.

Date of issuance: August 1, 1994

Effective date: August 1, 1994, with full implementation within 45 days.

Amendment No.: 102

Facility Operating License No. NPF-43: Amendment revises the Technical Specifications

Date of initial notice in Federal Register: June 8, 1994 (59 FR 29626) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 1, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Monroe County Library System, 3700 South Custer Road, Monroe, Michigan 48161.

Duke Power Company, Docket Nos. 50-369 and 50-370, McGuire Nuclear Station, Units 1 and 2, Mecklenburg County, North Carolina

Date of application for amendments: November 11, 1993, as supplemented on June 13, 1994

Brief description of amendments: The amendments revise the Technical Specification surveillance requirements for the emergency core cooling system subsystems.

Date of issuance: July 29, 1994

Effective date: July 29, 1994

Amendment Nos.: 145 and 127

Facility Operating License Nos. NPF-9 and NPF-17: Amendments revised the Technical Specifications.

Date of initial notice in Federal Register: April 13, 1994 (59 FR 17579) The June 13, 1994, letter provided clarifying and additional information that did not change the scope of the November 11, 1993, application and the initial proposed no significant hazards consideration determination.

The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated July 29, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Atkins Library, University of North Carolina, Charlotte (UNCC Station), North Carolina 28223

Duke Power Company, Docket Nos. 50-369 and 50-370, McGuire Nuclear Station, Units 1 and 2, Mecklenburg County, North Carolina

Date of application for amendments: May 5, 1994, as supplemented June 13, 1994.

Brief description of amendments: The amendments revise the Technical Specifications to increase Main Steam and Pressurizer Code Safety Valve Setpoint Tolerances.

Date of issuance: August 2, 1994

Effective date: August 2, 1994

Amendment Nos.: 146 and 128

Facility Operating License Nos. NPF-9 and NPF-17: Amendments revised the Technical Specifications.

Date of initial notice in Federal Register: June 21, 1994 (59 FR 32029) The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated August 2, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Atkins Library, University of North Carolina, Charlotte (UNCC Station), North Carolina 28223

Entergy Operations, Inc., Docket No. 50-382, Waterford Steam Electric Station, Unit 3, St. Charles Parish, Louisiana

Date of amendment request: December 14, 1993

Brief description of amendment: The amendment revised the Technical Specifications to revise the azimuthal power tilt limit from less than or equal to 0.10 (10%) to less than or equal to 0.03 (3%) and revises the action statement for control element assembly misalignment to allow 24 hours to restore the tilt to less than 3%.

Date of issuance: August 3, 1994

Effective date: August 3, 1994

Amendment No.: 97

Facility Operating License No. NPF-38: Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: January 19, 1994 (59 FR 2866) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 3, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: University of New Orleans Library, Louisiana Collection, Lakefront, New Orleans, Louisiana 70122.

**GPU Nuclear Corporation, et al.,
Docket No. 50-219, Oyster Creek
Nuclear Generating Station, Ocean
County, New Jersey**

Date of application for amendment:
April 6, 1994, as supplemented June 21,
1994

Brief description of amendment: The amendment eliminates the scram and main steam line isolation valve (MSIV) closure requirements associated with the main steam line radiation monitors (MSLRM). The amendment also eliminates the following related automatic isolation functions that are associated with the MSLRM scram and MSIV isolation: a) Main Steam Line Condenser Drain Valves, b) Emergency Condenser Drain Valves, c) Reactor Recirculation Loop Sample Valve, d) Instrumental Air Valves, and e) Condenser Pump Isolation.

Date of issuance: July 29, 1994

Effective date: As of the date of issuance to be implemented at the restart from refueling outage 15R.

Amendment No.: 169

Facility Operating License No. DPR-16. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: April 28, 1994 (59 FR 22003). The June 21, 1994, letter provided clarifying information that did not change the initial proposed no significant hazards consideration determination. The Commission's related evaluation of this amendment is contained in a Safety Evaluation dated July 29, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Ocean County Library, Reference Department, 101 Washington Street, Toms River, New Jersey 08753.

**GPU Nuclear Corporation, et al.,
Docket No. 50-289, Three Mile Island
Nuclear Station, Unit No. 1, Dauphin
County, Pennsylvania**

Date of application for amendment:
July 15, 1993.

Brief description of amendment: The amendment revises the plant Technical Specifications (TSs) on the Reactor Coolant Inventory Trending System (RCITS). The change is consistent with NUREG-1430 entitled "Standard Technical Specifications for Babcock and Wilcox Plants." The RCITS information will be available to the operator to enhance the operator's ability to understand and manage transients and events when needed.

Date of issuance: August 1, 1994

Effective date: As of its date of issuance, to be implemented within 30 days of issuance.

Amendment No.: 191

Facility Operating License No. DPR-50. Amendment revised the Technical Specifications. **Date of initial notice in Federal Register:** June 8, 1994 (59 FR 29626). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 1, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Government Publications Section, State Library of Pennsylvania, Walnut Street and Commonwealth Avenue, Box 1601, Harrisburg, Pennsylvania 17105.

**GPU Nuclear Corporation, et al.,
Docket No. 50-289, Three Mile Island
Nuclear Station, Unit No. 1, Dauphin
County, Pennsylvania**

Date of application for amendment:
February 10, 1994

Brief description of amendment: The amendment revises the TMI-1 Technical Specifications (TS) to revise specification 3.7.2.c, "Unit Electric Power System," to provide an option to testing an emergency diesel generator (EDG) when the redundant EDG is inoperable.

Date of issuance: July 25, 1994

Effective date: As of the date of issuance to be implemented within 30 days.

Amendment No.: 188

Facility Operating License No. DPR-50. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: June 22, 1994 (59 FR 32230). The Commission's related evaluation of this amendment is contained in a Safety Evaluation dated July 25, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Government Publications Section, State Library of Pennsylvania, Walnut Street and Commonwealth Avenue, Box 1601, Harrisburg, Pennsylvania 17105.

**GPU Nuclear Corporation, et al.,
Docket No. 50-289, Three Mile Island
Nuclear Station, Unit No. 1, Dauphin
County, Pennsylvania**

Date of application for amendment:
March 2, 1994

Brief description of amendment: The amendment revises the plant Technical Specifications to modify Operational Safety Instrumentation requirements to specify completion time which allows for performance of maintenance or surveillance within a reasonable time and to be consistent with the allowable outage time for other safety-related

equipment when only one train is affected.

Date of issuance: July 25, 1994

Effective date: As of the date of issuance to be implemented within 30 days after issuance.

Amendment No.: 189

Facility Operating License No. DPR-50. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: April 13, 1994 (59 FR 17600). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 25, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Government Publications Section, State Library of Pennsylvania, Walnut Street and Commonwealth Avenue, Box 1601, Harrisburg, Pennsylvania 17105.

**GPU Nuclear Corporation, et al.,
Docket No. 50-289, Three Mile Island
Nuclear Station, Unit No. 1, Dauphin
County, Pennsylvania**

Date of application for amendment:
March 11, 1994

Brief description of amendment: The amendment revises the plant Technical Specifications to specify an allowable outage time for the Emergency Feedwater Pumps during surveillance activities. It also changes the requirement to test redundant components for operability to a requirement to ensure operability based on verification of completion of appropriate surveillance activities.

Date of issuance: July 25, 1994

Effective date: As of the date of issuance to be implemented within 30 days of issuance.

Amendment No.: 190

Facility Operating License No. DPR-50. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: April 13, 1994 (59 FR 17601). The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 25, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Government Publications Section, State Library of Pennsylvania, Walnut Street and Commonwealth Avenue, Box 1601, Harrisburg, Pennsylvania 17105.

**Gulf States Utilities Company, Cajun
Electric Power Cooperative, and
Entergy Operations, Inc., Docket No.
50-458, River Bend Station, Unit 1,
West Feliciana Parish, Louisiana**

Date of amendment request: January
14, 1994

Brief description of amendment: The amendment revised TS Sections 3/4.3, "Instrumentation," 3/4.4.2, "Safety/Relief Valves," and associated Bases to increase the surveillance test intervals and allowable out-of-service times for various instruments.

Date of issuance: August 2, 1994

Effective date: August 2, 1994

Amendment No.: 74

Facility Operating License No. NPF-47. The amendment revised the Technical Specifications.

Date of initial notice in Federal Register: April 26, 1994 (59 FR 21787) The additional information contained in the supplemental letter dated July 15, 1994, was clarifying in nature and thus, within the scope of the initial notice and did not affect the staff's proposed no significant hazards consideration determination. The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 2, 1994. No significant hazards consideration comments received. No.

Local Public Document Room location: Government Documents Department, Louisiana State University, Baton Rouge, Louisiana 70803

Houston Lighting & Power Company, City Public Service Board of San Antonio, Central Power and Light Company, City of Austin, Texas, Docket Nos. 50-498 and 50-499, South Texas Project, Units 1 and 2, Matagorda County, Texas

Date of amendment request: March 16, 1994

Brief description of amendments: The amendments modified Figure 3.4-4, "Nominal Maximum Allowable PORV Setpoint for the Cold Overpressure System," for the cold overpressure mitigation system with a revised setpoint curve.

Date of issuance: August 3, 1994

Effective date: August 3, 1994, to be implemented within 31 days of issuance

Amendment Nos.: Unit 1 - Amendment No. 63; Unit 2 - Amendment No. 52

Facility Operating License Nos. NPF-76 and NPF-80. The amendments revised the Technical Specifications.

Date of initial notice in Federal Register: April 13, 1994 (59 FR 17601) The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated August 3, 1994. No significant hazards consideration comments received. No.

Local Public Document Room location: Wharton County Junior College, J. M. Hodges Learning Center, 911 Boling Highway, Wharton, Texas 77488

Northeast Nuclear Energy Company, Docket No. 50-245, Millstone Nuclear Power Station, Unit 1, New London County, Connecticut

Date of application for amendment: April 29, 1994

Brief description of amendment: The amendment changes the requirement for reactor operators in Table 6.2-1 from 2 to 3 for the RUN, STARTUP/HOT STANDBY and HOT SHUTDOWN conditions. In addition, two typographical corrections were made to page 6-4.

Date of issuance: August 2, 1994

Effective date: As of the date of issuance to be implemented within 60 days.

Amendment No.: 75

Facility Operating License No. DPR-21. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: June 22, 1994 (59 FR 32231) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 2, 1994. No significant hazards consideration comments received. No.

Local Public Document Room location: Learning Resource Center, Three Rivers Community-Technical College, Thames Valley Campus, 574 New London Turnpike, Norwich, Connecticut 06360.

Pacific Gas and Electric Company, Docket No. 50-133, Humboldt Bay Power Plant, Unit 3, Humboldt County, California

Date of application for amendment: October 8, 1993 (Reference HBL-93-058)

Brief description of amendment: This amendment modified the Technical Specifications (TS) incorporated in **Facility Operating License No.** DPR-7 as Appendix A by incorporating a title change into Section VII, Administrative Controls. This change reflects a plant organizational name change.

Date of issuance: July 26, 1994

Effective date: This license amendment is effective as of the date of its issuance and must be fully implemented no later than 30 days from the date of issuance.

Amendment No.: 27

Facility Operating License No. DPR-7: The amendment revised the TS.

Date of initial notice in Federal Register: January 5, 1994 (59 FR 624) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 26, 1994. No significant hazards consideration comments received. No.

Local Public Document Room location: Humboldt County Library, 636 F Street, Eureka, California 95501

Philadelphia Electric Company, Public Service Electric and Gas Company, Delmarva Power and Light Company, and Atlantic City Electric Company, Docket Nos. 50-277 and 50-278, Peach Bottom Atomic Power Station, Unit Nos. 2 and 3, York County, Pennsylvania

Date of application for amendments: October 27, 1993, as supplemented by letters dated April 29, 1994, and June 27, 1994

Brief description of amendments: These amendments revise the Unit 2 and Unit 3 Technical Specifications to allow one of the required on-shift senior reactor operators (SRO) to be combined with the required shift technical advisor (STA) position (i.e., dual-role SRO/STA position) as long as a minimum of three qualified individuals fill the SRO and STA positions.

Date of issuance: August 2, 1994

Effective date: August 2, 1994

Amendments Nos.: 191 and 196

Facility Operating License Nos. DPR-44 and DPR-56: Amendments revised the Technical Specifications.

Date of initial notice in Federal Register: December 8, 1993 (58 FR 64613) The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated August 2, 1994. No significant hazards consideration comments received. No.

Local Public Document Room location: Government Publications Section, State Library of Pennsylvania, (REGIONAL DEPOSITORY) Education Building, Walnut Street and Commonwealth Avenue, Box 1601, Harrisburg, Pennsylvania 17105.

Power Authority of The State of New York, Docket No. 50-286, Indian Point Nuclear Generating Unit No. 3, Westchester County, New York

Date of application for amendment: May 10, 1994

Brief description of amendment: The Technical Specifications amendment revised Section 3.1.C.3 and Table 4.1-1 of Appendix A of the Operating License. These changes require that the reactor coolant average temperature (T_{avg}) be no lower than 540°F during critical operation. Critical operation at T_{avg} less than 540°F requires operator response to restore T_{avg} to greater than or equal to 540°F within 15 minutes or be in hot shutdown within the following 15 minutes. Additionally, the change in Table 4.1-1 entitled, "Minimum Frequencies for Checks, Calibrations and Tests," adds the requirement for T_{avg} instrument check frequency to be reduced to 30 minutes when the T_{avg} banks are above zero steps.

Furthermore, the revision to the Bases indicates that the minimum temperature for criticality provides assurance that the reactor is operated within the bounds of the safety analyses. Also included is an administrative change to correct some typographical errors on page 3.1-25 of the Technical Specifications.

Date of issuance: July 25, 1994

Effective date: As of the date of issuance to be implemented within 30 days.

Amendment No.: 149

Facility Operating License No. DPR-64: Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: June 8, 1994 (59 FR 29630) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 25, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: White Plains Public Library, 100 Martine Avenue, White Plains, New York 10610.

Public Service Electric & Gas Company, Docket Nos. 50-272 and 50-311, Salem Nuclear Generating Station, Unit Nos. 1 and 2, Salem County, New Jersey

Date of application for amendments: May 3, 1994

Brief description of amendments: The amendments revised the Technical Specification (TS) for Combustible Gas Control (3/4.6.4.1) by changing the surveillance frequency for performing the channel functional test to once-per-quarter and the channel calibration to once-per-refueling. Also, the TS for the Auxiliary Feedwater System (3/4.7.1.2) were changed to reduce the surveillance frequency for performing pump operability tests to once-per-quarter on a staggered test basis. These changes are consistent with the provisions of Generic Letter 93-05, "Line-Item Technical Specifications Improvements to Reduce Surveillance Requirements For Testing During Power Operations."

Date of issuance: July 27, 1994

Effective date: July 27, 1994

Amendment Nos.: 153 and 134

Facility Operating License Nos. DPR-70 and DPR-75: These amendments revised the Technical Specifications.

Date of initial notice in Federal Register: June 8, 1994 (59 FR 29634) The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated July 27, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Salem Free Public Library, 112

West Broadway, Salem, New Jersey 08079

South Carolina Electric & Gas Company, South Carolina Public Service Authority, Docket No. 50-395, Virgil C. Summer Nuclear Station, Unit No. 1, Fairfield County, South Carolina

Date of application for amendment: March 11, 1994

Brief description of amendment: The amendment changes the Technical Specifications to delete TS Surveillance Requirement 4.8.4.1.a.3 that requires periodic retest of containment penetration overcurrent protection fuses and to remove references to containment penetration fuse testing from the TS Bases.

Date of issuance: July 29, 1994

Effective date: July 29, 1994

Amendment No.: 115

Facility Operating License No. NPF-12: Amendment revises the Technical Specifications.

Date of initial notice in Federal Register: May 12, 1994 (59 FR 24752) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 29, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Fairfield County Library, Garden and Washington Streets, Winnsboro, South Carolina 29180.

Southern Nuclear Operating Company, Inc., Docket No. 50-348, Joseph M. Farley Nuclear Plant, Unit 1, Houston County, Alabama.

Date of application for amendment: June 17, 1994

Brief description of amendment: The amendment changes the Technical Specifications to revise the nuclear enthalpy rise hot channel factor (F delta H) from equal to or less than 1.65 [1 plus 0.3(1-P)] to equal to or less than 1.70 [1 plus 0.3(1-P)] where P is a fraction of rated power. The amendment also revises the action statement to reflect guidance contained in the improved standard technical specifications.

Date of issuance: July 22, 1994

Effective date: July 22, 1994

Amendment No.: 109

Facility Operating License No. NPF-2: Amendment revises the Technical Specifications.

Date of initial notice in Federal Register: June 22, 1994 (59 FR 32249) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 22, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Houston-Love Memorial

Library, 212 W. Burdeshaw Street, Post Office Box 1369, Dothan, Alabama 36302

Tennessee Valley Authority, Docket Nos. 50-259, 50-260 and 50-296, Browns Ferry Nuclear Plant, Units 1, 2 and 3, Limestone County, Alabama

Date of application for amendments: August 25, 1992 (TS 321)

Brief description of amendments: The amendments delete reference to recirculation equalizer valves from the technical specifications. These components have been removed from Browns Ferry Unit 3, and are not used in Browns Ferry Units 1 and 2.

Date of issuance: August 4, 1994

Effective date: August 4, 1994

Amendment Nos.: 211, 226 and 184 *Facility Operating License Nos. DPR-33, DPR-52 and DPR-68:* Amendments revised the Technical Specifications.

Date of initial notice in Federal Register: October 28, 1992 (57 FR 48829) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 4, 1994. No significant hazards consideration comments received: None

Local Public Document Room location: Athens Public Library, South Street, Athens, Alabama 35611

Tennessee Valley Authority, Docket Nos. 50-327 and 50-328, Sequoyah Nuclear Plant, Units 1 and 2, Hamilton County, Tennessee

Date of application for amendments: June 17, 1993 (TS 93-08)

Brief description of amendments: The amendments revise the allowable values for the intermediate and source range neutron flux reactor trip setpoints.

Date of issuance: July 26, 1994

Effective date: July 26, 1994

Amendment Nos.: 185 and 177 *Facility Operating License Nos. DPR-77 and DPR-79:* Amendments revise the technical specifications.

Date of initial notice in Federal Register: August 4, 1993 (58 FR 41514) The Commission's related evaluation of the amendments are contained in a Safety Evaluation dated July 26, 1994. No significant hazards consideration comments received: None

Local Public Document Room location: Chattanooga-Hamilton County Library, 1101 Broad Street, Chattanooga, Tennessee 37402

Toledo Edison Company, Centerior Service Company, and The Cleveland Electric Illuminating Company, Docket No. 50-346, Davis-Besse Nuclear Power Station, Unit No. 1, Ottawa County, Ohio

Date of application for amendment: February 17, 1993

Brief description of amendment: This amendment increases the TS trip setpoint and its associated allowable value for containment high-radiation specified in TS Table 3.3-4 from "<2 x Background at RATED THERMAL POWER" to "<4 x Background at RATED THERMAL POWER."

Date of issuance: July 27, 1994

Effective date: As of the date of issuance to be implemented within 90 days.

Amendment No. 190

Facility Operating License No. NPF-3. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: June 23, 1993 (58 FR 34096) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated July 27, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: University of Toledo Library, Documents Department, 2801 Bancroft Avenue, Toledo, Ohio 43606.

TU Electric Company, Docket Nos. 50-445 and 50-446, Comanche Peak Steam Electric Station, Unit Nos. 1 and 2, Somervell County, Texas

Date of amendment request: February 14, 1994, as supplemented by letter dated April 29, 1994.

Brief description of amendments: The amendments increase the boron concentration limits for the Unit 2 refueling water storage tank and emergency core cooling system, and delete a footnote concerning refueling canal boron concentration during initial fuel load for both units.

Date of issuance: August 2, 1994

Effective date: August 2, 1994, to be implemented prior to startup for Cycle 2 for Comanche Peak Steam Electric Station, Unit 2.

Amendment Nos.: Unit 1 - Amendment No. 26; Unit 2 - Amendment No. 12

Facility Operating License Nos. NPF-87 and NPF-89. The amendments revised the Technical Specifications.

Date of initial notice in Federal Register: April 28, 1994 (59 FR 22015) The information contained in the April 29, 1994, letter was editorial in nature and thus, within the scope of the initial notice and did not affect the staff's proposed no significant hazards consideration determination. The Commission's related evaluation of the amendments is contained in a Safety Evaluation dated August 2, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: University of Texas at

Arlington Library, Government Publications/Maps, 701 South Cooper, P.O. Box 19497, Arlington, Texas 76019.

Union Electric Company, Docket No. 50-483, Callaway Plant, Unit 1, Callaway County, Missouri

Date of application for amendment: February 17, 1994, supplemented by letter dated May 18, 1994

Brief description of amendment: The amendment revises the Technical Specification 3/4.5.1 and associated Bases Section 3/4.5.1. A new Action Statement a. provides a 72-hour allowed outage time (AOT) for one accumulator inoperable due to boron concentration. The Action Statement b. AOT was changed to 24 hours. Surveillance Requirements 4.5.1.1.a.1 and 4.5.1.1.b were revised and 4.5.1.2 was deleted from the TS.

Date of issuance: August 5, 1994

Effective date: August 5, 1994 to be implemented within 30 days

Amendment No.: 91

Facility Operating License No. NPF-30. Amendment revised the Technical Specifications 3/4.5.1 and associated Bases Section 3/4.5.1.

Date of initial notice in Federal Register: March 30, 1994 (59 FR 14898) The additional information contained in the May 18, 1994, letter provided additional supplemental information that did not change the initial proposed no significant hazards consideration. The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 5, 1994. No significant hazards consideration comments received: No.

Local Public Document Room location: Callaway County Public Library, 710 Court Street, Fulton, Missouri 65251.

Virginia Electric and Power Company, et al., Docket Nos. 50-338 and 50-339, North Anna Power Station, Units No. 1 and No. 2, Louisa County, Virginia

Date of application for amendments: April 19, 1994

Brief description of amendments: The amendments revise the NA-1&2 Technical Specifications surveillance frequency requirements for control rod motion testing from once per 31 days to once per 92 days.

Date of issuance: July 28, 1994

Effective date: July 28, 1994

Amendment Nos.: 185 and 166

Facility Operating License Nos. NPF-4 and NPF-7: Amendments revised the Technical Specifications.

Date of initial notice in Federal Register: May 25, 1994 (59 FR 27070) The Commission's related evaluation of the amendments is contained in a Safety

Evaluation dated July 28, 1994. No significant hazards consideration comments received: No.

Local Public Document Room

location: The Alderman Library, Special Collections Department, University of Virginia, Charlottesville, Virginia 22903-2498.

Virginia Electric and Power Company, Docket Nos. 50-280 and 50-281, Surry Power Station, Unit Nos. 1 and 2, Surry County, Virginia.

Date of application for amendments: April 19, 1994

Brief description of amendments: These amendments modify the surveillance frequency of the control rod motion testing from monthly to quarterly

Date of issuance: August 2, 1994

Effective date: August 2, 1994

Amendment Nos.: 192 and 192

Facility Operating License Nos. DPR-32 and DPR-37: Amendments revised the Technical Specifications.

Date of initial notice in Federal Register: May 25, 1994 (59 FR 27070) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 2, 1994. No significant hazards consideration comments received: No

Local Public Document Room location: Swem Library, College of William and Mary, Williamsburg, Virginia 23185

Washington Public Power Supply System, Docket No. 50-397, Nuclear Project No. 2, Benton County, Washington

Date of application for amendment: April 1, 1993

Brief description of amendment: The amendment modifies the Technical Specifications to add inservice inspection requirements for reactor coolant system piping in accordance with Generic Letter 88-01, "NRC Position on Intergranular Stress Corrosion Cracking (IGSCC) in BWR Austenitic Stainless Steel Piping." In addition, the amendment corrects an administrative error in a TS that references a table listing high/low pressure interface valve leakage pressure monitors.

Date of issuance: July 28, 1994

Effective date: 30 days after the date of issuance.

Amendment No.: 130

Facility Operating License No. NPF-21: The amendment revised the Technical Specifications.

Date of initial notice in Federal Register: May 12, 1993 (58 FR 28065) The Commission's related evaluation of the amendment is contained in a Safety

Evaluation dated July 28, 1994. No significant hazards consideration comments received: No.

Local Public Document Room
location: Richland Public Library, 955 Northgate Street, Richland, Washington 99352

Washington Public Power Supply System, Docket No. 50-397, Nuclear Project No. 2, Benton County, Washington

Date of application for amendment: February 17, 1994, supplemented by letter dated May 13, 1994.

Brief description of amendment: The amendment changes the Technical Specifications (TS) 10-year hydrostatic testing requirements. The changes (1) add a special test exception for inservice leak testing and hydrostatic testing, (2) add a new minimum reactor vessel metal pressure-temperature curve for less than or equal to eight effective full power years, and (3) delete Table B 3/4.4.6-1, "Reactor Vessel Toughness," from the TS bases.

Date of issuance: May 27, 1994

Effective date: May 27, 1994

Amendment No.: 122

Facility Operating License No. NPF-21: The amendment revised the Technical Specifications.

Date of initial notice in Federal Register: March 30, 1994 (59 FR 14902) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated May 27, 1994. No significant hazards consideration comments received: No.

Local Public Document Room
location: Richland Public Library, 955 Northgate Street, Richland, Washington 99352

Wisconsin Public Service Corporation, Docket No. 50-305, Kewaunee Nuclear Power Plant, Kewaunee County, Wisconsin

Date of application for amendment: December 1, 1993

Brief description of amendment: The amendment revises the Kewaunee Nuclear Power Plant (KNPP) Technical Specifications (TS) by incorporating technical and administrative changes to TS 3.10, Control Rod and Power Distribution Limits. The changes eliminate specifications for fuel designs no longer used at Kewaunee, specify required actions to be taken upon exceeding control bank insertion limits, and revise the limits for Departure from Nucleate Boiling (DNB) related parameters to assure operation within the assumptions of the Updated Safety Analysis Report (USAR) analyses.

Date of issuance: August 3, 1994

Effective date: As of the date of issuance to be implemented within 30 days.

Amendment No.: 110
Facility Operating License No. DPR-43. Amendment revised the Technical Specifications.

Date of initial notice in Federal Register: February 2, 1994 (59 FR 4949) The Commission's related evaluation of the amendment is contained in a Safety Evaluation dated August 3, 1994. No significant hazards consideration comments received: No.

Local Public Document Room
location: University of Wisconsin Library Learning Center, 2420 Nicolet Drive, Green Bay, Wisconsin 54301.

Notice Of Issuance Of Amendments To Facility Operating Licenses And Final Determination Of No Significant Hazards Consideration And Opportunity For A Hearing (Exigent Public Announcement Or Emergency Circumstances)

During the period since publication of the last biweekly notice, the Commission has issued the following amendments. The Commission has determined for each of these amendments that the application for the amendment complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendment.

Because of exigent or emergency circumstances associated with the date the amendment was needed, there was not time for the Commission to publish, for public comment before issuance, its usual 30-day Notice of Consideration of Issuance of Amendment, Proposed No Significant Hazards Consideration Determination, and Opportunity for a Hearing.

For exigent circumstances, the Commission has either issued a **Federal Register** notice providing opportunity for public comment or has used local media to provide notice to the public in the area surrounding a licensee's facility of the licensee's application and of the Commission's proposed determination of no significant hazards consideration. The Commission has provided a reasonable opportunity for the public to comment, using its best efforts to make available to the public means of communication for the public to respond quickly, and in the case of telephone comments, the comments have been recorded or transcribed as

appropriate and the licensee has been informed of the public comments.

In circumstances where failure to act in a timely way would have resulted, for example, in derating or shutdown of a nuclear power plant or in prevention of either resumption of operation or of increase in power output up to the plant's licensed power level, the Commission may not have had an opportunity to provide for public comment on its no significant hazards consideration determination. In such case, the license amendment has been issued without opportunity for comment. If there has been some time for public comment but less than 30 days, the Commission may provide an opportunity for public comment. If comments have been requested, it is so stated. In either event, the State has been consulted by telephone whenever possible.

Under its regulations, the Commission may issue and make an amendment immediately effective, notwithstanding the pendency before it of a request for a hearing from any person, in advance of the holding and completion of any required hearing, where it has determined that no significant hazards consideration is involved.

The Commission has applied the standards of 10 CFR 50.92 and has made a final determination that the amendment involves no significant hazards consideration. The basis for this determination is contained in the documents related to this action. Accordingly, the amendments have been issued and made effective as indicated.

Unless otherwise indicated, the Commission has determined that these amendments satisfy the criteria for categorical exclusion in accordance with 10 CFR 51.22. Therefore, pursuant to 10 CFR 51.22(b), no environmental impact statement or environmental assessment need be prepared for these amendments. If the Commission has prepared an environmental assessment under the special circumstances provision in 10 CFR 51.12(b) and has made a determination based on that assessment, it is so indicated.

For further details with respect to the action see (1) the application for amendment, (2) the amendment to Facility Operating License, and (3) the Commission's related letter, Safety Evaluation and/or Environmental Assessment, as indicated. All of these items are available for public inspection at the Commission's Public Document Room, the Gelman Building, 2120 L Street, NW., Washington, DC 20555, and at the local public document room for the particular facility involved.

The Commission is also offering an opportunity for a hearing with respect to the issuance of the amendment. By September 16, 1994, the licensee may file a request for a hearing with respect to issuance of the amendment to the subject facility operating license and any person whose interest may be affected by this proceeding and who wishes to participate as a party in the proceeding must file a written request for a hearing and a petition for leave to intervene. Requests for a hearing and a petition for leave to intervene shall be filed in accordance with the Commission's "Rules of Practice for Domestic Licensing Proceedings" in 10 CFR Part 2. Interested persons should consult a current copy of 10 CFR 2.714 which is available at the Commission's Public Document Room, the Gelman Building, 2120 L Street, NW., Washington, DC 20555 and at the local public document room for the particular facility involved. If a request for a hearing or petition for leave to intervene is filed by the above date, the Commission or an Atomic Safety and Licensing Board, designated by the Commission or by the Chairman of the Atomic Safety and Licensing Board Panel, will rule on the request and/or petition; and the Secretary or the designated Atomic Safety and Licensing Board will issue a notice of a hearing or an appropriate order.

As required by 10 CFR 2.714, a petition for leave to intervene shall set forth with particularity the interest of the petitioner in the proceeding, and how that interest may be affected by the results of the proceeding. The petition should specifically explain the reasons why intervention should be permitted with particular reference to the following factors: (1) the nature of the petitioner's right under the Act to be made a party to the proceeding; (2) the nature and extent of the petitioner's property, financial, or other interest in the proceeding; and (3) the possible effect of any order which may be entered in the proceeding on the petitioner's interest. The petition should also identify the specific aspect(s) of the subject matter of the proceeding as to which petitioner wishes to intervene. Any person who has filed a petition for leave to intervene or who has been admitted as a party may amend the petition without requesting leave of the Board up to 15 days prior to the first prehearing conference scheduled in the proceeding, but such an amended petition must satisfy the specificity requirements described above.

Not later than 15 days prior to the first prehearing conference scheduled in the

proceeding, a petitioner shall file a supplement to the petition to intervene which must include a list of the contentions which are sought to be litigated in the matter. Each contention must consist of a specific statement of the issue of law or fact to be raised or controverted. In addition, the petitioner shall provide a brief explanation of the bases of the contention and a concise statement of the alleged facts or expert opinion which support the contention and on which the petitioner intends to rely in proving the contention at the hearing. The petitioner must also provide references to those specific sources and documents of which the petitioner is aware and on which the petitioner intends to rely to establish those facts or expert opinion. Petitioner must provide sufficient information to show that a genuine dispute exists with the applicant on a material issue of law or fact. Contentions shall be limited to matters within the scope of the amendment under consideration. The contention must be one which, if proven, would entitle the petitioner to relief. A petitioner who fails to file such a supplement which satisfies these requirements with respect to at least one contention will not be permitted to participate as a party.

Those permitted to intervene become parties to the proceeding, subject to any limitations in the order granting leave to intervene, and have the opportunity to participate fully in the conduct of the hearing, including the opportunity to present evidence and cross-examine witnesses. Since the Commission has made a final determination that the amendment involves no significant hazards consideration, if a hearing is requested, it will not stay the effectiveness of the amendment. Any hearing held would take place while the amendment is in effect.

A request for a hearing or a petition for leave to intervene must be filed with the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, DC 20555, Attention: Docketing and Services Branch, or may be delivered to the Commission's Public Document Room, the Gelman Building, 2120 L Street, NW., Washington, DC 20555, by the above date. Where petitions are filed during the last 10 days of the notice period, it is requested that the petitioner promptly so inform the Commission by a toll-free telephone call to Western Union at 1-(800) 248-5100 (in Missouri 1-(800) 342-6700). The Western Union operator should be given Datagram Identification Number N1023 and the following message addressed to (Project Director):

petitioner's name and telephone number, date petition was mailed, plant name, and publication date and page number of this Federal Register notice. A copy of the petition should also be sent to the Office of the General Counsel, U.S. Nuclear Regulatory Commission, Washington, DC 20555, and to the attorney for the licensee.

Nontimely filings of petitions for leave to intervene, amended petitions, supplemental petitions and/or requests for a hearing will not be entertained absent a determination by the Commission, the presiding officer or the Atomic Safety and Licensing Board that the petition and/or request should be granted based upon a balancing of the factors specified in 10 CFR 2.714(a)(1)(i)-(v) and 2.714(d).

Commonwealth Edison Company,
Docket Nos. STN 50-454 and STN 50-455, Byron Station, Unit Nos. 1 and 2, Ogle County, Illinois

Date of application for amendments:
August 2, 1994

Brief description of amendments: The amendments revise the Technical Specifications by adding a footnote that recognizes that through the end of cycle 6, the Unit 1, loop B wide range hot leg indication at the remote shutdown panel is inoperable.

Date of issuance: August 5, 1994

Effective date: August 5, 1994

Amendment Nos.: 63 and 63

Facility Operating License Nos. NPF-37 and NPF-66. The amendments revised the Technical Specifications. Public comments requested as to proposed no significant hazards consideration: No. The Commission's related evaluation of the amendments, finding of emergency circumstances, and final determination of no significant hazards consideration are contained in a Safety Evaluation dated August 5, 1994.

Attorney for licensee: Michael I. Miller, Esquire; Sidley and Austin, One First National Plaza, Chicago, Illinois 60690

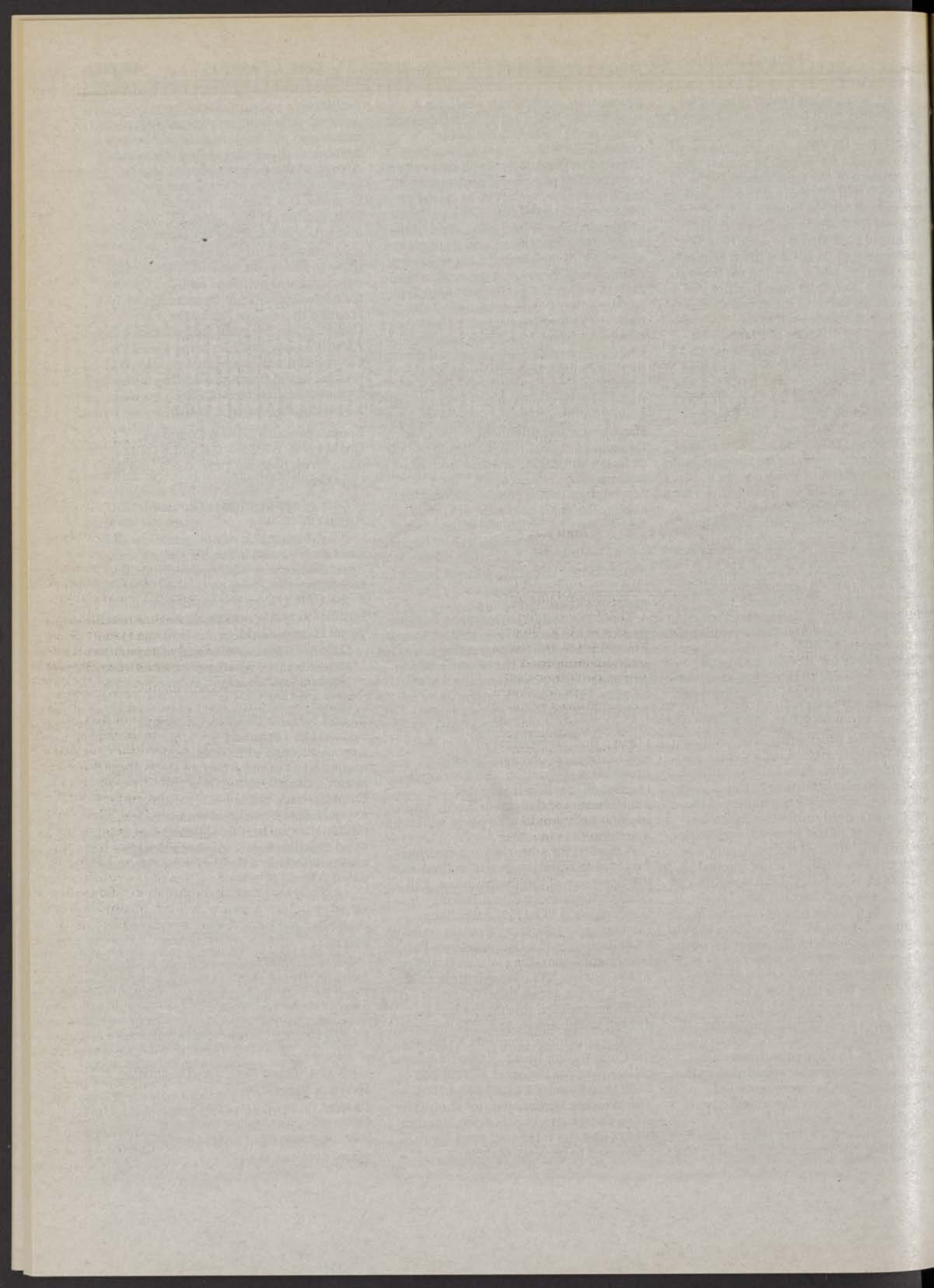
Local Public Document Room location: Byron Public Library, 109 N. Franklin, P.O. Box 434, Byron, Illinois 61010.

NRC Project Director: Robert A. Capra
Dated at Rockville, Maryland, this 10th day of August 1994.

For The Nuclear Regulatory Commission
Steven A. Varga,

Director, Division of Reactor Projects - I/II
Office of Nuclear Reactor Regulation
[Doc. 94-20006 Filed 8-16-94 8:45 am]

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Wednesday
August 17, 1994

Environmental Protection Agency

Part III

**Environmental
Protection Agency**

Final Report: Principles of Neurotoxicity
Risk Assessment; Notice

ENVIRONMENTAL PROTECTION AGENCY

[FRL-5050-8]

Final Report: Principles of Neurotoxicity Risk Assessment

AGENCY: U.S. Environmental Protection Agency.

ACTION: Final Document.

SUMMARY: The U.S. Environmental Protection Agency is publishing a document entitled *Final Report: Principles of Neurotoxicity Risk Assessment*, which was prepared by the Working Party on Neurotoxicology under the auspices of the Subcommittee on Risk Assessment of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET). The purpose of this report is to articulate a view of neurotoxicology that scientists generally hold in common today and to draw on this understanding to generate a series of general principles that can be used to establish guidelines for assessing neurotoxicity risk. It is not the intent of this report to provide specific directives for how neurotoxicity risk assessment should be performed. The intent of this document is to provide the scientific basis for the development of a cogent strategy for neurotoxicity risk assessment.

SUPPLEMENTARY INFORMATION: This document is the result of the combined efforts of senior scientists of 13 Federal agencies comprising the ad hoc Interagency Committee on Neurotoxicology, including the Agency for Toxic Substances and Disease Registry, Center for Food Safety and Applied Nutrition, Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Consumer Product Safety Commission, Department of Agriculture, Department of Defense, Environmental Protection Agency, National Center for Toxicological Research, National Institutes of Health, National Institute for Occupational Safety and Health, and National Toxicology Program. Discussions were held under the auspices of the Working Party on Neurotoxicology of the Subcommittee on Risk Assessment of the Federal Coordinating Council for Science, Engineering, and Technology. The draft report, a product of the Working Party on Neurotoxicology, contains six chapters: an introduction, an overview of the discipline of neurotoxicology, a review of methods for assessing human neurotoxicity, a review of methods for assessing animal neurotoxicity, an

overview of principles of neurotoxicity risk assessment, and a general summary.

The draft report was prepared in view of the decision-making processes currently used by many regulatory agencies relating to neurotoxicity risk assessment. It is intended that the principles reviewed in this document will serve as the basis for consistent regulatory neurotoxicity guidelines to be used by Federal agencies to meet their respective legislative mandates. This document is not meant to be used to perform risk assessment nor does it recommend one approach or strategy. The document reviews the science of neurotoxicology and attempts to formulate general assumptions and principles that could lead to such approaches or strategies.

The draft report has undergone interagency review under the auspices of the Subcommittee on Risk Assessment of FCCSET. Public comments received were used in the preparation of the final report by the Working Party on Neurotoxicology.

Dated: August 9, 1994.

Ken Sexton,

Director, Office of Health Research.

Final Report: Principles of Neurotoxicology Risk Assessment

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1. Introduction

1.1. Background

Over the years, agencies and programs have been established to deal with hazardous substances, with a focus on deleterious long-term effects, including noncancer endpoints such as neurotoxicity (Reiter, 1987). Recent evidence indicates that exposure to neurotoxic agents may constitute a significant health problem (WHO, 1986;

OTA, 1990; chapter 2). Table 1-1 lists the four Federal regulatory agencies with authority to regulate either exposure to or use of chemicals and that require data reporting on assessment of hazards. Regulatory bodies vary greatly in their mandate to require approval of chemicals prior to entering the marketplace and to regulate subsequent exposure (Fisher, 1980) (Table 1-2). The Occupational Safety and Health Administration (OSHA) cannot require chemical testing by the manufacturer whereas all other agencies can. Only the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have authority for premarketing testing of chemicals (i.e., FDA for drugs and food additives and EPA for pesticides). EPA can, under some circumstances, require premarket testing of industrial and agricultural chemicals. The Consumer Product Safety Commission (CPSC) regulates a number of consumer products including household chemicals and fabric treatments. Laws administered by CPSC require cautionary labeling on all hazardous household products whether the hazard is based on acute or chronic effects. These laws also provide the authority to ban hazardous products and to ask for data in support of product labeling.

TABLE 1-1.—MAJOR REGULATORY AGENCIES

Agency	Statute and sources covered
Food and Drug Administration (FDA) A unit of the Department of Health and Human Services with authority over the regulation of medical and veterinary drugs; foods and food additives; cosmetics.	Food, Drug, and Cosmetics Act for food additives; color in cosmetics; medical devices; animal drugs of medical and feed additives.
Occupational Safety and Health Administration (OSHA) A unit of the Department of Labor that regulates workplace conditions ..	Occupational Safety and Health Act covers toxic chemicals in the workplace.
Environmental Protection Agency (EPA). Independent agency (i.e., not part of a Cabinet department); administers a number of diverse laws concerned with human health and the environment.	Toxic Substances Control Act requires premanufacture evaluation of all new chemicals (other than foods, food additives, drugs, pesticides, alcohol, tobacco); allows EPA to regulate existing chemical hazards not sufficiently controlled under other laws. Clean Air Act requires regulation of hazardous air pollutants. Federal Water Pollution Control Act governs toxic water pollutants. Safe Drinking Water Act covers drinking water contaminants. Federal Insecticide, Fungicide, and Rodenticide Act covers pesticides. Resource Conservation and Recovery Act covers hazardous wastes. Marine Protection Research and Sanctuaries Act covers ocean dumping.
Consumer Product Safety Commission (CPSC). Regulates a variety of consumer products including household chemicals and fabric treatments.	Federal Hazardous Substances Act covers "toxic" household products. Consumer Product Safety Act covers dangerous consumer products. Poison Prevention Packaging Act covers packaging of dangerous children's products. Lead-Based Paint Poison Prevention Act covers use of lead paint in federally assisted housing.

TABLE 1-2.—AUTHORITIES FOR TOXICITY TESTING

Agency	Law	Coverage	Authorities		
			Premarketing approval	Testing by manufacturer	Reporting of data
FDA	Food, Drug, and Cosmetics Act	Drugs and foods	x	x	x
		Food additives and cosmetics	x	x	
EPA	Federal Insecticide, Fungicide, and Rodenticide Act	Pesticides	x	x	x
	Toxic Substances Control Act	Industrial chemicals	¹ x	x	x
	Clean Air Act	Air pollutants		x	x
	Resource Conservation and Recovery Act	Industrial waste		x	x
OSHA	Occupational Safety and Health Act	Occupational exposure			x
CPSC	Federal Hazardous Substances Act	Consumer products		x	
	Consumer Product Safety Act	Consumer products			x

¹ Can require testing based on available data.

1.2. Purpose of This Report

The purpose of this document is to: (1) articulate a view of neurotoxicity that scientists generally hold in common today and (2) draw upon this understanding to compose, as was done here by senior scientists from a number of Federal agencies, a series of general principles that can be used to establish general guidelines for assessing neurotoxicity risk. It is not the intent of this report to provide specific directives to agencies with respect to their own approach for neurotoxicity risk assessment. This document is intended to provide the scientific basis for the development of a cogent strategy for neurotoxicology risk assessment as needed by each agency.

Because of present gaps in understanding, the principles contained in this document are based on the best judgment of those involved in writing this document, as well as statements of what is generally accepted as fact. There has been, however, an attempt to distinguish where possible between the different types of information presented.

The principles contained in this document can serve as the basis for consistent regulatory neurotoxicology guidelines that the Federal agencies can tailor to meet the requirements of the legislative acts they are charged to implement. This document should be viewed broadly as part of an ongoing process within the Federal Government to periodically update and review the current scientific understanding and regulatory utility of neurotoxicity risk assessment.

This document is the result of the combined efforts of senior scientists from the following Federal health-related units, operating under the direction of the Office of Science and Technology Policy (OSTP):

Agency for Toxic Substances and Disease Registry (ATSDR)
Center for Biologics Evaluation and Research (CBER), FDA
Center for Drug Evaluation and Research (CDER), FDA
Center for Food Safety and Applied Nutrition (CFSAN), FDA
Consumer Product Safety Commission
Department of Agriculture (USDA)
Department of Defense (DoD)
Environmental Protection Agency
National Center for Toxicological Research (NCTR), FDA
National Institutes of Health (NIH)
National Institute for Occupational Safety and Health
National Toxicology Program (NTP)

1.3. Context of This Report

This document was prepared in light of a decision-making process used by many regulatory agencies pertaining to the assessment of neurotoxicity risks posed by chemical agents. The scientific basis for such assessment can be best understood by examining the decision-making process in some detail.

Risk can be thought of as being composed of two aspects, each of which can be addressed by science, i.e., hazard and exposure assessment. Although other definitions have been used historically, this document conforms to present usage. Hazard generally refers to the toxicity of a substance and is deduced from a wide array of data, including those from epidemiological studies or controlled clinical trials in humans, short- and long-term toxicological studies in animals, and studies of mechanistic information and structure-activity relationships. Exposure generally refers to the amount of a substance with which people come in contact. The risk in a quantitative risk assessment is estimated by considering the results of the exposure and hazard

assessments. As either the hazard or exposure approaches zero, the risk also approaches zero.

As a first step in assessing the neurotoxic risk associated with the use of a particular chemical substance, the qualitative evidence that a given chemical substance is likely to be a human neurotoxicant must be evaluated. In this step, as in the whole process, a number of assumptions and approximations must be made in order to deal with inherent limitations found in the existing data bases. Then, estimates of human exposure and distribution of exposures likely to be encountered in the population are made. In the absence of dose-response relationships in humans, one or more methods for estimating the dose-response relationship including doses below those generally used experimentally must also be evaluated. Finally, the exposure assessment is combined with the dose-response relationship to generate an estimate of risk. The various ways in which these steps are conducted and combined and their attendant uncertainties constitute what is generally referred to as "neurotoxicity risk assessment."

Some legislation calls for action in the presence of any risk. Other forms of legislation use the concept of unreasonable risk, defined in some acts as a condition in which the risks outweigh the benefits. A spectrum of regulatory responses, from simply informing the public of a risk through restricted use to a complete ban, may be available to bring the risks and benefits into appropriate balance.

This document does not perform a risk assessment nor does it suggest that one method of neurotoxicology risk assessment is better than another. Rather, it attempts to review the science

of chemical neurotoxicology and develops from this review a set of general principles. It is not a comprehensive review nor a document written for the lay public; this document is a semitechnical review that evaluates the impact of scientific findings of the last decade on general assumptions or principles important to risk assessment. This is based on the belief that elucidation of the basic mechanisms underlying neurotoxicity and the identification of neurotoxic agents and conditions, when coupled to research aimed at identifying and characterizing the problems caused by such agents, should provide the best scientific bases for making sound and reasonable judgments. These overlapping approaches to evaluating the problems of neurotoxicology should form a strong foundation for decision-making.

1.4. Content of This Report

Including the Introduction (chapter 1), this document contains six chapters. Chapter 2 provides an overview of the discipline of neurotoxicology. It is important to understand the scope of the problem as it relates to neurotoxicology, including: (1) Definitions of neurotoxicity and adverse effect, (2) examples of neurotoxicity and incidents of exposure, and (3) Federal response to neurotoxicology. Chapter 2 also discusses the basic principles of toxicology that apply generally to the evaluation of neurotoxicity. Issues such as dose, exposure, target site, and the intended use of the chemical are discussed, as are principles of pharmacodynamics, chemical interactions, and the concept of threshold. Chapter 2 also lays the neurobiological basis for understanding how and where chemicals can affect the nervous system and provides examples of such chemical types. Finally, chapter 2 discusses special considerations for neurotoxicology including the issue of susceptible populations, the blood brain barrier, and the limited capability of the nervous system to repair following chemical insult.

Chapter 3 examines methods for assessing human neurotoxicity. Neurologic evaluations, neuropsychological testing, and applicability of methods used in clinical evaluations and case studies are discussed in this chapter. Epidemiologic study designs, endpoints, and methods are also discussed, as well as problems of causal inference and applications and limitations of epidemiologic and field study methods for risk assessment. Chapter 3 also describes human laboratory exposure studies, including methods for assessing neurobehavioral

function, self-report methods for assessing subjective states, and a number of other methodological issues. This chapter also discusses the comparability of human and animal laboratory methods and special considerations in human neurotoxicity assessments.

Chapter 4 assesses methods for evaluating animal neurotoxicity. Discussed in this chapter is the role that animal models play in the assessment of chemicals for neurotoxicity, the validity of animal models, and experimental design considerations in animal neurotoxicological studies. Also included in this chapter is a discussion of tier-testing approaches in chemical evaluations. Specific endpoints used in animal neurotoxicological studies are also discussed, including methods for neurobehavioral, neurophysiological, neuroanatomical, and neurochemical assessments. Developmental neurotoxicology and in vitro neurotoxicology are also described in this chapter.

Chapter 5 of this document discusses principles of neurotoxicity risk assessment. This chapter evaluates the generic assumptions in neurotoxicity risk assessment, ending with a discussion of uncertainty reduction and identification of knowledge gaps.

Chapter 6 is a general summary of the material presented in the first five chapters.

2. Overview of Neurotoxicology

2.1. Scope of the Problem

2.1.1. Introduction

Chemicals are an integral part of our lives, with the capacity to both improve as well as endanger our health. The general population is exposed to chemicals with neurotoxic properties in air, water, foods, cosmetics, household products, and drugs used therapeutically or illicitly. Naturally occurring neurotoxins, such as fish and plant toxins, present other hazards. During the daily life of an ordinary person, there is a multitude of exposures, both voluntary and unintentional, to neuroactive substances. Under conditions of multiple exposures, identifying the substance responsible for an adverse response may be difficult. The EPA's inventory of toxic chemicals is greater than 65,000 and increasing yearly. Concerns have been raised about the toxicological data available for many compounds used commercially (NRC, 1984).

It is not known how many chemicals are neurotoxic to humans. However, estimates have been made for subsets of

substances. A large percentage of the more than 500 registered active pesticide ingredients are neurotoxic to varying degrees. Of 588 chemicals listed by the American Conference of Government and Industrial Hygienists (ACGIH), 167 affected the nervous system or behavior (Anger, 1984; CDC, 1986). Using a generally broad definition of neurotoxicity, Anger (1990a) estimated that of the approximately 200 chemicals to which 1 million or more American workers are exposed, more than one-third may have adverse effects on the nervous system at some level of exposure. Anger (1984) also recognized neurotoxic effects as one of the ten leading workplace disorders. In addition, a number of therapeutic substances, including some anticancer and antiviral agents and abused drugs, can cause adverse or neurotoxicological side effects (OTA, 1990). It has been estimated that there is inadequate toxicological information available for more than three-fourths of the 12,860 chemicals with a production volume of 1 million pounds or more (NRC, 1984). It should be noted, however, that estimates concerning the number of neurotoxins vary widely. O'Donoghue (1989), for example, reported that of 488 compounds assessed in his chemical evaluation process, only 2.7% had effects on the nervous system.

2.1.2. Examples of Neurotoxicity and Incidents of Exposure

There is a long-standing history associating certain neurological and psychiatric disorders to exposure to a toxin or chemical of an environmental origin (OTA, 1990) (Table 2-1). Lead is one of the earliest examples of a neurotoxic chemical with widespread exposure. This metal is widely distributed with major sources of inorganic lead including industrial emissions, lead-based paints, food, beverages, and the burning of leaded gasolines. Organic lead compounds such as tetraethyl lead have been reported to produce a toxic psychosis (Cassells and Dodds, 1946). If exposure occurs at relatively low levels during development, lead can cause a variety of neurobehavioral problems, learning disorders, and altered mental development (Bellinger et al., 1987; Needleman, 1990). Over the years, Federal Government regulations have been developed to decrease human exposure to lead, and as a goal an intervention level of 10 µg/dcl whole blood has been recommended (CDC, 1991). Lead exposure in the United States has decreased significantly during the last several years.

TABLE 2-1.—HUMAN NEUROTOXIC EXPOSURES

Year(s)	Location	Substance	Comments
370 B.C.	Greece	Lead	Lead toxicity recognized in mining industry.
1st century A.D.	Rome	Lead	Vapors recognized as toxic.
1837	Scotland	Manganese	Chronic manganese poisoning described.
1924	United States (New Jersey)	Tetraethyl lead	Workers suffer neurologic symptoms.
1930	United States (South-east)	Tri-o-cresylphosphate (TOCP)	Chemical contaminant added to Ginger Jake, an alcoholic beverage substitute; more than 5,000 paralyzed, 20,000 to 100,000 affected.
1930's	Europe	Apiol	Drug containing TOCP causes 60 cases of neuropathy.
1932	United States (California)	Thallium	Contaminated barley laced with thallium sulfate poisons family, causing neurologic symptoms.
1937	South Africa	TOCP	Paralysis develops after use of contaminated cooking oil.
1946	England	Tetraethyl lead	Neurologic effects observed in people cleaning gasoline tanks.
1950's	Japan (Minamata)	Methylmercury	Fish and shellfish contaminated with mercury are ingested, causing neurotoxicity.
1950's	France	Organotin	Medication (Stalnin) containing diethyltin diiodide results in poisoning.
1950's	Morocco	Manganese	Miners suffer chronic manganese intoxication.
1950's	Guam	Cycad	Ingestion of plants associated with amyotrophic lateral sclerosis and Parkinson-like syndrome.
1956	Turkey	Hexachlorobenzene	Hexachlorobenzene causes poisoning.
1956	Japan	Clioquinol	Drug causes neuropathy.
1959	Morocco	TOCP	Cooking oil contaminated with lubricating oil causes poisoning.
1960	Iraq	Methylmercury	Mercury-treated seed grain causes neurotoxicity.
1964	Japan	Methylmercury	Methylmercury neurotoxicity.
1968	Japan	PCBs	Polychlorinated biphenyls are leaked into rice oil, causing neurotoxicity.
1969	Japan	n-Hexane	Neuropathy due to n-hexane exposure.
1969	United States (New Mexico)	Methylmercury	Fungicide-treated grain results in alkyl mercury poisoning.
1971	United States	Hexachlorophene	Hexachlorophene-containing disinfectant is found to be toxic to nervous system.
1971	Iraq	Methylmercury	Methylmercury used as fungicide to treat seed grain causes poisoning.
1972	France	Hexachlorophene	Hexachlorophene poisoning of children.
1973	United States (Ohio)	Methyl n-butylketone	Fabric production plant employees exposed to MnBK solvent suffer polyneuropathy.
1974-1975	United States (Virginia)	Chlordecone (Keptone)	Chemical plant employees exposed to insecticide suffer severe neurologic problems.
1976	United States (Texas)	Leptophos (Phosvel)	At least nine employees suffer serious neurologic problems after exposure to insecticide.
1977	United States (California)	Dichloropropene (Telone II)	People hospitalized after exposure to pesticide.
1979-1980	United States (Texas)	2-t-Butylazo-2-hydroxy-5-methylhexane (BHMH) (Lucel-7)	Employees of manufacturing plant experience serious neurologic problems.
1980's	United States	Methylphenyltetrahydropyridine (MPTP)	Impurity in synthesis of illicit drug causes Parkinson's disease-like effects.
1981	Spain	Toxic oil	People ingesting toxic substance in oil suffer severe neuropathy.
1983-84	United States	Vitamin B ₆	Excessive intake, causes sensory neuropathy, numbness, parathesia, and motor dysfunction.
1985	United States and Canada	Aldicarb	People experience neuromuscular deficits after ingestion of contaminated melons.
1987	Canada	Domoic acid	Ingestion of mussels contaminated with domoic acid causes illnesses.
1988	India	TOCP	Ingestion of adulterated rapeseed oil cause polyneuritis.
1989	United States	L-tryptophan-containing products	Ingestion of a chemical contaminant associated with the manufacture of L-tryptophan results in eosinophilia-myalgia syndrome.
1991	Nigeria	Scopoletin	Natural component of gari caused neuropathy associated with optic atrophy and ataxia.

Mercury compounds are potent neurotoxic substances and have caused a number of human poisonings, with symptoms of vision, speech, and coordination impairments (Chang, 1980). Erethism, a syndrome with such neurologic features as tremor and behavioral symptoms as anxiety, irritability, and pathologic shyness, is seen in people exposed to elemental mercury (Bidstrup, 1964). One major

incidence of human exposure occurred in the mid-1950's when a chemical plant near Minamata Bay, Japan, discharged mercury as part of waste sludge. An epidemic of mercury poisoning developed when the local inhabitants consumed contaminated fish and shellfish. Congenitally affected children displayed a progressive neurological disturbance resembling cerebral palsy and manifested other

neurological problems as well. In 1971, an epidemic occurred in Iraq from methylmercury used as a fungicide to treat grain (OTA, 1990).

Manganese is used in metal alloys and has been proposed to replace lead in gasoline. It is an essential dietary substance for normal body functioning yet parenteral exposure to manganese can be neurotoxic, producing a dyskinetic motor syndrome similar to Parkinson's disease (Cook et al., 1974).

Exposed miners in several countries have suffered from "manganese madness" characterized by hallucinations, emotional instability, and numerous neurological problems. Long-term manganese toxicity produces muscle rigidity and staggering gait similar to that seen in patients with Parkinson's disease (Politis et al., 1980).

A Parkinsonian-like syndrome was also observed in people who accidentally ingested 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston et al., 1983). MPTP was a byproduct of a meperidine derivative sold illicitly as "synthetic heroin."

Organic solvents are encountered frequently in occupational settings. Most solvents are volatile, i.e., they can be converted from a liquid to a gaseous state and readily inhaled by the worker. They are also lipid soluble and readily accumulate in the fat deposits of the exposed organism. An example of a solvent exposure in humans is carbon disulfide. Workers exposed to high levels of this solvent were found to have an increased frequency of depression and suicide (Seppäläinen and Haltia, 1980). Furthermore, repeated exposure to organic solvents is suspected of producing chronic encephalopathy. Workers exposed to methyl-n-butyl ketone, a dye solvent and cleaning agent, displayed peripheral nervous system neuropathy involving degeneration of nerve fibers (Spencer and Schaumburg, 1980). Solvents including ether, ketones, alcohols, and various combinations are commonly used in glues, cements, and paints and when inhaled can be neurotoxic. Repeated abuse of such solvents can lead to permanent neurological effects due to severe and permanent loss of nerve cells (OTA, 1990).

Pesticides are one of the most commonly encountered classes of neurotoxic substances. These can include insecticides (used to control insects), fungicides (for blight and mildew), rodenticides (for rodents such as rats, mice, and gophers), and herbicides (to control weeds). Active ingredients are combined with so-called inert substances to make thousands of different pesticide formulations. Workers who are overexposed to pesticides may display obvious signs of poisoning, including tremors, weakness, ataxia, visual disturbances, and short-term memory loss (Ecobichon and Joy, 1982). Chlordecone exposure results in nervousness and tremors (Cannon et al., 1978). The organophosphorous insecticides have neurotoxic properties and account for approximately 40 percent of registered pesticides. A

delayed neurotoxicity can be seen as a result of exposure to certain organophosphate pesticides, producing irreversible loss of motor function and an associated neuropathology (Ecobichon and Joy, 1982).

Organophosphate and carbamate insecticides are known to interfere with a specific enzyme, acetylcholinesterase (AChE) (Davis and Richardson, 1980). Paralysis has also been reported following consumption of nonpesticide organophosphate products such as tri-o-cresylphosphate (TOCP).

Neurotoxicities in humans, domestic livestock, and poultry associated with fungal toxins (mycotoxins) have been well documented (Kurata, 1990; Aibara, 1986; Wyllie and Morehouse, 1978). Mycotoxins not only have a negative economic effect on animal production, but they also represent a definite threat to human health. Mycotoxins occur in forages, field crops, and grains used for livestock; they also are incorporated into cereals, grains, and grain-based products used for human consumption. Therefore, human exposure may occur either through direct consumption of these products or secondarily through consumption of meat, milk, or eggs. An example of human exposure to fungal toxins is *Claviceps purpurea*- or *C. paspali*-infected wheat, barley, and oats used for bread and as a dietary supplement for livestock. These fungal toxins are notorious for producing the gangrenous and convulsive forms of the disease known as "ergotism" (Bove, 1970). These fungi are in the family *Clavicipitaceae* and produce a group of compounds known as ergot alkaloids, which have neurotropic, uterotonic, and vasoconstrictive activities. They may act as dopamine agonists or serotonin antagonists, and also block alpha-adrenergic receptors. Since there are numerous naturally occurring ergot alkaloids, this represents only part of their pharmacopoeia (Berde and Schield, 1978). These alkaloids are highly toxic and cause both acute and chronic poisonings. Although guidelines now limit the amount of *Claviceps*-contaminated, or "ergot"-contaminated, grains, these compounds may enter human food sources through secondary mechanisms. Other fungi associated with ergot-like syndromes in livestock include *Acremonium lolii* (Gallagher et al., 1984) and *A. coenophialum* (Thompson and Porter, 1990).

Cyclopiazonic acid (CPA) is an indole tetramic acid produced by *Aspergillus flavus*, *A. oryzae*, *Penicillium cyclopium*, and *P. camemberti*. This mycotoxin is suspected of causing "kodua poisoning" in humans who

consumed kodo millet seed in India (Rao and Husain, 1985). *Fusarium moniliforme* is a common fungal infection in corn (Bacon et al., 1992) and directly related to neurotoxic syndrome in horses known as equine leukoencephalomalacia (ELEM).

Natural plant toxins also represent a health risk to both livestock and humans. Movement toward limited uses of herbicides, fungicides, and no-till agricultural practices increases the possibility of noxious weeds and weed seeds being incorporated into food products. Ergot alkaloids also are produced by morning glories (*Ipomea violacea*) and may be incorporated into soybeans, corn, peas, etc., during harvest. Export regulations limit morning glory-contaminated soybeans because of the hallucinogenic and other effects produced by ergot alkaloids. Jimson weed (*Datura stramonium*), another weed incorporated into agricultural commodities, produced scopolamine, hyocyanine, and atropine, all of which have parasympatholytic (anticholinergic) activities.

Recently, an outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid, an excitotoxin, was reported (Perl et al., 1990).

2.1.3. Federal Response

In the United States, several agencies, including EPA, FDA, OSHA, CPSC, NIOSH, and ATSDR, have been given the mandate to regulate or evaluate public exposure to toxic chemicals (Tilson, 1989).

2.1.3.1. Food and Drug Administration.

The FDA has the authority to regulate the use of food and color additives as well as to determine whether or not various foods are unsafe for human consumption because of adulteration by environmental contaminants. The manufacturer must supply adequate data to establish the safety of the food additives. Before marketing approval, the potential toxicity of proposed food and color additives is established in a battery of animal toxicity studies. During all of these studies, clinical signs of toxicity, including abnormal behavior, are monitored and abnormalities recorded. At the termination of these studies, tissues from all organs, including the brain, are sectioned and evaluated for both gross and histopathological changes, in addition to being evaluated for their clinical chemistry and hematology. None of the routinely required tests is specifically designed to assess neurotoxicity. If neurotoxic effects are detected during any of the standard

toxicity tests, however, they must be reported. Specific neurotoxicity testing may then be required. The FDA is currently revising its guidelines for the safety assessment of direct food and color additives to include neurotoxicity as a routine element in toxicological testing.

The FDA is also authorized to regulate substances in food considered to be poisonous or deleterious. Unavoidable environmental contaminants in food fall into this category. The FDA determines a level at which the risks from realistically possible intakes are negligible or acceptable. Based on this risk assessment, an action level or tolerance is established. Once the action level or tolerance is formally established, the FDA may take appropriate action to restrict adulterated food from the market if these standards are exceeded.

The FDA is responsible for assessing the toxicity of human therapeutic products. Many products have been shown to produce adverse effects on the nervous system at standard therapeutic doses as well as at higher doses. Before marketing approval is given, the toxicity of potential new products is assessed. A battery of animal toxicity study parameters relevant to the nervous system, including gross behavioral observation and gross and histopathological examination of the nervous tissue, are evaluated. This information is used to help guide the surveillance of human subjects for adverse effects that are assessed during clinical trials.

2.1.3.2. Occupational Safety and Health Administration.

OSHA has been given the responsibility to ensure that the working environment is a safe and healthy place of employment. In the early 1970's, OSHA adopted the existing Federal standards, most of which were developed under the Walsh-Healy Act (including the 1968 ACGIH Threshold Limit Values), and approximately 20 consensus standards of the American National Standards Institute (ANSI) as Permissible Exposure Limits (PELs). Of the 393 remaining original PELs, 145 were set in part to protect the individual from neurotoxic effects.

Since the adoption of the initial standards, OSHA has issued new or revised health standards or work practices for 23 substances. Of these, the one concerning lead was based in part on nervous system effects. Four other compounds, inorganic arsenic, acrylonitrile, ethylene oxide, and 1,2-dibromo-3-chloropropane, were cited as causing various disturbances in the

nervous system, but the standards for these were based primarily on carcinogenic effects.

In 1989, OSHA updated 428 exposure limits for air contaminants. Of these, 25 substances were categorized by OSHA as "substances for which limits are based on avoidance of neuropathic effects." In addition, 24 substances were included in the category "substances for which limits are based on avoidance of narcosis." However, OSHA stated that the categorization was intended as a tool to manage the large number of substances being regulated and not to imply that the category selected identified the most sensitive or the exclusive adverse health effects of that substance.

2.1.3.3. National Institute for Occupational Safety and Health.

The Occupational Safety and Health Act established NIOSH as a Public Health Service (PHS) agency to develop and recommend criteria for prevention of disease and hazardous conditions in the workplace. NIOSH also performs research on occupational health issues and conducts worksite evaluations of suspected hazards. OSHA and the Mine Safety and Health Administration (MSHA) use NIOSH recommendations in the promulgation of new or revised health and safety standards.

In establishing recommended exposure limits (RELs) for chemicals, NIOSH examines all relevant scientific information about a given compound and attempts to identify exposure limits that will protect all workers from adverse effects. NIOSH has recommended standards for approximately 644 chemicals or classes of chemicals. For 214 (33 percent) of these, neurotoxicity was cited as a health effect considered when formulating the REL (NIOSH, 1992).

2.1.3.4. Environmental Protection Agency.

The Toxic Substances Control Act (TSCA) and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) provide the legislative authority for EPA to require data collection for premarket approval of chemicals. Under section 5 of TSCA, after a manufacturer has notified EPA of its plans to produce a "new" chemical that has not yet been listed on the inventory, EPA has the responsibility to assess possible health hazards. Potential neurotoxicity is included in the health hazards assessment. If there are reasons to suspect neurotoxicologic effects (e.g., from structure-activity analysis, information in the literature, or data submitted by the manufacturer), EPA

can issue a test rule requiring the manufacturer to develop data directed toward these effects. At the same time, EPA can restrict the chemical or prohibit it entirely from entering commerce until the required data are submitted and reviewed. In addition, for "old" chemicals (under section 4 of TSCA), if EPA suspects neurotoxicity, a test rule would be the mechanism used for obtaining the data. Many other statutes provide authority to regulate chemicals through the setting of standards, including the Clean Air Act, Clean Water Act, and Safe Drinking Water Act.

Neurotoxicity is recognized as a health effect of concern under FIFRA, and there are neurotoxicity testing requirements for premarketing submission of data to EPA for registration of a pesticide under FIFRA.

2.1.3.5. Consumer Product Safety Commission.

The CPSC is an independent Federal regulatory agency with jurisdiction over most consumer products. Most chemical hazards are regulated under the Federal Hazardous Substances Act (FHSA) administered by CPSC. The FHSA requires appropriate cautionary labeling on all hazardous household products (hazards include chronic toxicity such as neurotoxicity). While the FHSA does not require premarket registration, a manufacturer is required to assess the hazards of a product prior to marketing and assure that it is labeled with all necessary cautionary information. The FHSA also bans children's products that are hazardous and provides the CPSC with the authority to ban other hazardous products.

2.1.3.6. Agency for Toxic Substances and Disease Registry.

ATSDR has a mission to prevent or mitigate adverse effects to both human health and the quality of life resulting from exposure to hazardous substances in the environment. The ATSDR publishes a National Priority List (NPL) of hazardous substances that are found at National Priority Waste Sites. The order of priority is based on an algorithm, taking into consideration frequency with which substances are found at NPL sites, toxicity, and potential for human exposure; this list is reranked on a yearly basis. So far, 129 toxicological profiles have been developed for the priority hazardous substances, and 92 substances have a profile with a neurological health effect endpoint (HAZDAT, 1992). Neurotoxicity has been selected by the ATSDR to be one of the seven high-

priority health conditions resulting from exposure to environmental toxicants.

2.2. Basic Toxicological Considerations for Neurotoxicity

2.2.1. Basic Toxicological Principles

A chemical must enter the body, reach the tissue target site(s), and be maintained at a sufficient concentration for a period of time in order for an adverse effect to occur. Not all chemicals have the same level of toxicity; some may be very toxic in small amounts while others may have little effect even at extremely high amounts. Thus, the dose-response relationship is a major concept in determining the toxicity of a specific substance. Other factors in determining toxicity include the physical and chemical properties of the substance, the route and level of exposure, the susceptibility of the target tissue, and the health, gender, and age of the exposed individual.

Once the toxic substance has entered the body, usually through the lungs (inhalation), the skin (absorption), or the gastrointestinal tract (ingestion), it is partitioned into various body tissues where it can act on its target sites. The substance is eliminated from the bloodstream by the process of accumulation into the various sites in the body, with the liver and kidney being major sites of accumulation of toxic substances. This is thought to be associated with these organs' large blood capacity and major role in elimination of substances from the body. Lipophilic chemicals accumulate in lipid-rich areas of the body and present a significant potential problem for the nervous system. The nervous system is unique in its high percentage content of lipid (50 percent of dry weight) and may be particularly vulnerable to such chemicals. The site or sites of accumulation for a specific toxic substance may or may not be the primary sites of action. Examples include two known neurotoxicants, carbon monoxide in the red blood cells and lead in the bone. It must be noted that some substances are not distributed throughout the body, partially as a function of their insolubility, polarity, or molecular weight.

The effect that a substance has will generally depend on the body burden or level in the tissue and duration of exposure. The time course of the levels is determined by several factors, including the amount at time of exposure, duration of exposure, and metabolic fate of the chemical. The study of such metabolic processes, pharmacokinetics, has demonstrated

complex patterns in the absorption, distribution, possible biotransformation, and elimination of various substances (Klaassen, 1980).

Many substances are removed by the kidney and excreted through the urine. The liver can detoxify substances like organic lead, which are excreted from the liver into the bile and then the small intestines, bypassing the blood and kidney. Lipophilic toxic substances are primarily removed from the body through feces and bile, and water-soluble metabolites are removed in the urine, through the skin, and through expiration into the air. Biotransformation is a biochemical process that converts a substance into a different chemical compound, allowing it to be excreted more easily. Substances are more easily removed if they are biotransformed into a more hydrophilic compound. Biotransformation can either aid in the detoxification of a substance or produce a more toxic metabolite. Therefore, the original substance may not be the substance that is producing the toxicity on the nervous system or any other system. Thus, several factors must be taken into consideration when evaluating the potential neurotoxicity of a chemical. They include the pharmacokinetics of the parent compound, the target tissue concentrations of the parent chemical or its bioactivated proximate toxicant, the uptake kinetics of the parent chemical or metabolite into the cell and/or membrane interactions, and the interaction of the chemical or metabolite with presumed receptor sites.

2.2.2. Basic Neurotoxicological Principles

Neurotoxicity can be manifest as a structural or functional adverse response of the nervous system to a chemical, biological, or physical agent (Tilson, 1990b). It is a function of both the property of the agent and a property of the nervous system itself. Neurotoxicity refers broadly to the adverse neural responses following exposure to chemical or physical agents (e.g., radiation) (Tilson, 1990b). Adverse effects include any change that diminishes the ability to survive, reproduce, or adapt to the environment. Neuroactive substances may also impair health indirectly by altering behavior in such a way that safety is decreased in the performance of numerous activities. Toxicity can occur at any time in the life cycle, from conception through senescence, and its manifestations can change with age. The range of responses can vary from temporary responses following acute exposures to delayed responses following acute or chronic

exposure to persistent responses. Neurotoxicity may or may not be reversible following cessation of exposure. The responses may be graded from transient to fatal and there may be different responses to the same neurotoxicant at different dose levels but similar responses to exposure to different agents. Displays of a neurotoxic response may be progressive in nature, with small deficits occurring early in exposure and developing to become more severe over time. Expression of neurotoxicity can encompass multiple levels of organization and complexity including structural, biochemical, physiological, and behavioral measurements.

Caution must be exercised in labeling a substance neurotoxic. The intended use and effect of the chemical, the dose, exposure scenario and whether or not the chemical acts directly or indirectly on the nervous system, must be taken into consideration. A substance that may be neurotoxic at a high concentration may be safe and beneficial at a lower concentration. For example, vitamin A, vitamin B6, are required in the diet in trace amounts, yet all result in neurotoxicity when consumed in large quantities. Pharmaceutical agents may also have adverse effects at high dose levels or where the beneficial effects outweigh the adverse side effects. For example, antipsychotic drugs have allowed many people suffering from schizophrenia to lead relatively normal lives; however, chronic prescribed use of some of these drugs may result in severe tardive dyskinesia characterized by involuntary movements of the face, tongue, and limbs. Other examples include toxic neuropathies induced by chemotherapeutic agents like cis-platinum, toxic anticholinergic effects of high doses of tricyclic antidepressants, disabling movement disorders in patients treated with anti-Parkinsonian agents and major tranquilizers, and hearing loss and balance disruption triggered by certain antibacterials (Serman and Schaumburg, 1980). Drugs of abuse such as ethanol also have neurotoxic potential. Opiates such as heroin may lead to dependence, which is considered to be a long-term adverse alteration of nervous system functioning. Simultaneous exposure to drugs or toxic agents may produce toxic interactions either in the environment or occupational settings. For example, exposure to noise and certain antibiotics can exacerbate the loss of hearing function (Boettcher et al., 1987; Lim, 1986; Bhattacharyya and Dayal, 1984).

The nervous system is a highly complex and integrated organ. It is

possible that nonlinear dose-response relationships or a threshold effect could exist for some agents. It has been hypothesized that the nervous system has a reserve capacity that masks subtle damage and any exposure that does not overcome this reserve capacity may not reach the threshold and no observable impairment will be evident (Tilson and Mitchell, 1983). However, the functional reserve may be depleted over time and the manifestations of toxicity may be delayed in relationship to the exposure. The reserve may be depleted by a number of factors including aging, stress, or chronic exposure to an environmental insult, in which case functioning will eventually be impaired and toxicity will become apparent. If a number of events occur simultaneously, the response is progressive in nature, or there is a long latency between exposure and manifestation of toxicity, the identification of a single cause of the functional impairment may not be possible.

2.3. Basic Neurobiological Principles

2.3.1. Structure of the Nervous System

The nervous system is composed of two parts: the central nervous system (CNS) and the peripheral nervous system (PNS) (Spencer and Schaumburg, 1980). Within the nervous system, there exist predominantly two general types of cells—nerve cells (neurons) and glial cells. Neurons have many of the same structures found in every cell of the body; they are unique, however, in that they have axons and dendrites, extensions of the neuron along which nerve impulses travel. The structure of the neuron consists of a cell body, 10 to 100 μ m in diameter, containing a nucleus and organelles for the synthesis of various components necessary for the cell's functioning, e.g., proteins and lipids. There are numerous branch patterns of elongated processes, the dendrites, that emanate from the cell body and increase the neuronal surface area available to receive inputs from other sources. Neurons communicate with each other by releasing chemical signals onto specific surface regions, receptors, of the other neuron. The axon is a process specialized for the conduction of nerve impulses away from the cell toward the terminal synapses and eventually toward other cells (neurons, muscle cells, or gland cells).

Neurons are responsible for the reception, integration, transmission, and storage of information (Raine, 1989). Certain nerve cells are specialized to respond to particular stimuli. For example, chemoreceptors in the mouth

and nose send information about taste and smell to the brain. Cutaneous receptors in the skin are involved in the sensation of pressure, pain, heat, cold, and touch. In the retina, the rods and cones sense light. In general, the length of the axon is tens to thousands of times greater than the cell body diameter. For example, the cell body whose processes innervate the muscles in the human foot is found in the spinal cord at the level of the middle back. The axons of these cells are more than a meter in length. Many, but not all, axons are surrounded by the layers of membrane from the cytoplasmic process of glial cells. These layers are called myelin sheaths and are composed mostly of lipid. In the PNS, the myelin sheaths are formed by Schwann cells, while in the CNS the sheaths are formed by the oligodendroglia. The myelin sheath formed by one glial cell covers only a short length of the axon. The entire length of the axon is ensheathed in myelin by numerous glial cells. Between adjacent glial sheaths, a very short length of bare axon exists called the node of Ranvier. In unmyelinated axons, a nerve impulse must travel in a continuous fashion down the entire length of the nerve. The presence of myelin accelerates the nerve impulse by up to 100 times by allowing the impulse to jump from one node to the next in a process called "saltatory conduction."

The nerve cells of the PNS are generally found in aggregates called ganglia. The brain and spinal cord make up the CNS and the neurons are segregated into functionally related aggregates called nuclei. They synthesize and secrete neurotransmitters, which are specialized chemical messengers that interact with receptors of other neurons in the communication process. Various nuclei together with the interconnecting bundles of axonal fibers are functionally related to one another to form higher levels of organization called systems. For example, there is the motor system, the visual system, and the limbic system. At the base of the brain, several small nuclei in the hypothalamus form the neuroendocrine system, which plays a critical role in the control of the body's endocrine (hormone-secreting) glands. Nerve cells in the hypothalamus secrete chemical messengers into a short loop of blood vessels that carries the messengers to the pituitary gland which, in turn, releases chemical messengers into the general circulation. These pituitary messengers regulate other glands (e.g., the thymus and the gonads). The entire system maintains a

state of optimal physiological function for all of the body's organ systems.

2.3.2. Transport Processes

All types of cells must transport proteins and other molecular components from their site of production near the nucleus to the other sites in the cell (Hammerschlag and Brady, 1989). Neurons are unique in that the neuronal cell body must maintain not only the functions normally associated with its own support, but it must also provide support to its various processes. This support may require transport of material over relatively vast distances. Delivery of necessary substances by intracellular transport down the axon (axonal transport) represents a supply line that is highly vulnerable to interruption by toxic chemicals. In addition, the integrity of the function of the neuronal cell body is often dependent on a supply of trophic factors from the cells that it innervates. These factors are continually supplied to the neural cells by the process of retrograde axonal transport, often as a process of normal exchange between two or more cells. They play a significant factor in the normal growth and maintenance of the neural cells, and a continual supply of certain trophic factors is necessary for cell functioning.

The majority of axonal transport occurs along longitudinally arranged fiber tracks called neurofilaments. This movement along neurofilaments requires energy in the form of oxidative metabolism. Toxicants that interfere with this metabolism or that disrupt the spatial arrangement or production of neurofilaments may block axonal transport and can produce neuropathy (Lowndes and Baker, 1980). This can be seen following exposure to many substances, such as n-hexane and methyl n-butyl ketone as well as the drugs vincristine, vinblastine, and taxol. Acrylamide produces a dying-back axonopathy but by an alternative mechanism involving altered axonal transport.

2.3.3. Ionic Balance

The axonal membrane is semipermeable to positively and negatively charged ions (mostly potassium, sodium, and chloride) within and outside of the axon. There are several enzyme systems that maintain an ionic balance that changes following depolarization of the membrane (Davies, 1968). This is maintained only by the continual active transport of ions across the membrane, which requires an expenditure of energy. The nerve impulse is a traveling

wave of depolarization normally originating from the cell body; however, in sensory neurons it originates at the terminal receptive end of specialized axons (Davies, 1968). The wave is continued by openings in the membrane that allow ions to rush into the axon. This sudden change in the charge across the axon's membrane is the nerve impulse. It is an amplified depolarization that reaches the threshold value and spreads down the axon from one length to another until the next length of membrane reaches the threshold value. It continues in this fashion until it reaches the synaptic terminal regions. There are a number of varieties of membrane channels (e.g., calcium) that rapidly open and close during impulse generation; the common ones are the sodium and potassium channels. They are very small and allow only ions of a certain size to pass. Several classes of drugs (e.g., local anesthetics) and natural toxins (e.g., tetrodotoxin) inhibit nerve impulse conduction by blocking these channels.

2.3.4. Neurotransmission

The terminal branches of the axon end in small enlargements called synaptic "boutons." It is from these boutons that chemical messengers will be released in order to communicate with the target cell at the point of interaction, the synapse (Hammerschlag and Brady, 1989). When the nerve impulse reaches the terminal branches of the axon, it depolarizes the synaptic boutons. This depolarization causes the release of the chemical messengers (neurotransmitters and neuromodulators) stored in vesicles in the axon terminal (Willis and Grossman, 1973). Classical neurotransmitters include serotonin, dopamine, acetylcholine, and norepinephrine and are typically secreted by one neuron into the synaptic cleft where they are on the postsynaptic membrane. Neuropeptides, however, may travel long distances through the bloodstream to receptors on distant nerve cells or in other tissues. Following depolarization, the amount of secretion is dependent on the number of nerve impulses that reach the synaptic bouton, i.e., the degree of depolarization. The chemical messengers diffuse across the synaptic cleft or into the intraneuronal space and bind to receptors on adjacent nerve cells or effector organs, thus triggering biochemical events that lead to electrical excitation or inhibition.

When information is transmitted from nerves to muscle fibers, the point of interaction is called the neuromuscular junction and the interaction leads to contraction or relaxation of the muscle.

When the target is a gland cell, the interaction leads to secretion. Synaptic transmission between neurons is slightly more complicated, but still dependent on the opening and closing of ion channels in the membrane. The binding of the messenger to the receptor of the receiving cell can lead to either the excitation or inhibition of the target cell. At an excitatory synapse, the neurotransmitter-receptor interaction leads to an opening in certain ion-specific channels. The charged ions that move through these opened chambers carry a current that serves to depolarize the cell membranes. At inhibitory synapses, the interaction leads to an opening in a different type of ion-specific channel that produces an increase in the level of polarization (hyperpolarization). The sum of all the depolarizing and hyperpolarizing currents determines the transmembrane potential and when a threshold level of depolarization is reached at the axon's initial segment, a nerve impulse is generated and begins to travel down the axon.

The duration of neurotransmitter action is primarily a function of the length of time it remains in the synaptic cleft. This duration is very short due to specialized enzymes that quickly remove the transmitter either by degrading it or by reuptake systems that transport it back into the synaptic bouton. A toxic substance may disrupt this process in several different ways. It is important that the duration of the effect of synaptically released chemical messengers be limited. Some neurotoxicants, e.g., cholinesterase-inhibiting organophosphorous pesticides, inhibit the enzyme (AChE), which serves to terminate the effect of the neurotransmitter (acetylcholine) on its target. The result is an overstimulation of the target cell. Other substances, particularly biological toxins, are able to interact with the receptor molecule and mimic the action of the neurotransmitter. Some toxic substances, like neuroactive pharmaceuticals, may interfere with the synthesis of a particular neurotransmitter, while others may block the neurotransmitter's access to its receptor molecule.

2.4. Types of Effects on the Nervous System

The normal activity of the nervous system can be altered by many toxic substances. A variety of adverse health effects can be seen ranging from impairment of muscular movement to disruption of vision and hearing to memory loss and hallucinations (WHO, 1986; Anger, 1984, 1990). Toxic

substances can alter both the structure and the function of cells in the nervous system. Structural alterations include changes in the morphology of the cell and its subcellular structures. In some cases, agents produce neuropathic conditions that resemble naturally occurring neurodegenerative disorders in humans (Calne et al., 1986). Cellular alterations can include the accumulation, proliferation, or rearrangement of structural elements (e.g., intermediate filaments, microtubules) or organelles (mitochondria) as well as the breakdown of cells. By affecting the biochemistry and/or physiology of a cell, a toxic substance can alter the internal environment of any neural cell. Intracellular changes can result from oxygen deprivation (anoxia) because neurons require relatively large quantities of oxygen due to their high metabolic rate.

Many times the response of the nervous system to a toxic substance can be a slow degeneration of the nerve cell body or axon that may result in permanent neuronal damage. Substances can act as a cytotoxicant after having been transported into the nerve terminal. A complete loss of nerve cells can occur following exposure to a number of toxic substances. Sensory nerve cells may be lost following treatment with megavitamin doses of vitamin B6; hippocampal neurons undergo degeneration with trimethyltin and trimethyl lead poisoning; motor nerve cells are affected in cycad toxicity, which has been loosely linked to Guam-ALS-Parkinsonism dementia. Acute carbon monoxide poisoning can produce a delayed, progressive deterioration over a period of weeks of portions of the nervous system that may lead to psychosis and death. Substances such as mercury and lead can cause central nervous system dysfunction. In children, mercury intoxication can cause degeneration of neurons in the cerebellum and can lead to tremors, difficulty in walking, visual impairment, and even blindness. Lead affects the cortex of the immature brain, resulting in mental retardation.

At the cellular level, a substance might interfere with cellular processes like protein synthesis, leading to a reduced production of neurotransmitters and brain dysfunction (Bondy, 1985). Nicotine and some insecticides mimic the effects of the neurotransmitter acetylcholine. Organophosphorous compounds, carbamate insecticides, and nerve gases act by inhibiting AChE, the enzyme that inactivates the neurotransmitter acetylcholine. This results in a buildup

of acetylcholine and can lead to loss of appetite, anxiety, muscle twitching, and paralysis. Amphetamines stimulate the nervous system by releasing and blocking reuptake of the neurotransmitters norepinephrine and dopamine from nerve cells. Cocaine affects the release and reuptake of norepinephrine, dopamine, and serotonin. Both drugs can cause paranoia, hyperactivity, aggression, high blood pressure, and abnormal heart rhythms. Opium-related drugs such as morphine and heroin act at specific opioid receptors in the brain, producing sedation, euphoria, and analgesia. They also tend to slow the heart rate and cause nausea, convulsions, and slow breathing patterns. Other substances can alter the synthesis and release of specific neurotransmitters and activate their receptors in specific neuronal pathways. They may perturb the system by overstimulating receptors, blocking transmitter release and/or inhibiting transmitter degradation, or blocking reuptake of neurotransmitter precursors.

Also at the cellular level, the flow of ions such as calcium, sodium, and potassium across the cell membrane may be changed and the transmission of information between nerve cells altered. A substance may interfere with the ionic balance of a neuron. Organophosphate and carbamate insecticides produce autonomic dysfunction and organochlorine insecticides increase sensorimotor sensitivity, produce tremors and in some cases cause seizures and convulsions (Ecobichon and Joy, 1982). Lindane, DDT, pyrethroids, and trimethyltin also produce convulsions. Conversely, solvents act to raise the threshold for eliciting seizures or act to reduce the severity or duration of the elicited convulsions.

The role of excitatory amino acid (EAA)-mediated synaptic activation is critical for normal function of the CNS. Because endogenous EAA-mediated synaptic transmission is a widespread excitatory system in the brain and is involved in the process of learning and memory, the issue of the effects of endogenous and exogenous EAA-related toxicity has broad implications for both CNS morbidity and mortality in humans. Much of the injury and neuronal death associated with toxicity is mediated by receptors for excitatory amino acids, especially glutamic acid. When applied in sufficient excess from either endogenous or exogenous sources, EAAs have profound neurotoxic effects that can result in the destruction of neurons and, as a consequence, lead to acute phase confusion, seizures, and generalized

weakness or to persistent impairments such as memory loss (Ghoi, 1988).

A final common path in the activation of these receptor classes is an increase in free cytosolic Ca^{++} that can result in the release and activation of intracellular enzymes (which break down the cytoskeleton) and in further release of glutamate, both of which can be cytotoxic (Choi, 1988). Critical to an understanding of the etiopathology associated with at least some of the neurotoxic degeneration may be the link that impaired energy metabolism could have with excitotoxic neuronal death. It is likely that reduced oxidative metabolism results in the partial depolarization of resting membrane potential, the activation of ionotropic membrane receptor/channels, and the influx of Ca^{++} or its release from intracellular stores.

The nervous system is dependent on an extensive system of blood vessels and capillaries to deliver large quantities of oxygen and nutrients as well as to remove toxic waste products. Damage to the capillaries in the brain can lead to the swelling characteristic of encephalopathy. This can be seen following exposure to higher concentrations of lead. Other metals (e.g., cadmium, thallium, and mercury) and organotin (e.g., trimethyltin) cause rupturing of vessels that can also result in encephalopathy.

One large aspect of function that may be affected by neurotoxicants is behavior, which is the product of various sensory, motor, and associative functions of the nervous system. Neurotoxic substances can adversely affect sensory or motor functions, disrupt learning and memory processes, or cause detrimental behavioral effects; however, the underlying mechanisms for these effects have yet to be determined. Although changes may be subtle, the assessment of behavior may serve as a robust means of monitoring the well-being of the organism (Tilson and Cabe, 1978).

2.5. Special Considerations

2.5.1. Susceptible Populations

Everyone is at a certain level of risk of being adversely affected by neurotoxic substances. Individuals of certain age groups, health states, and occupations, however, may be at a greater level of risk. Fetuses, children, the elderly, workers in occupations involving exposure to relatively high levels of toxic chemicals, and persons who abuse drugs are among those in high-risk groups. Neurotoxic substances may exacerbate existing neurological or psychiatric disorders in a population.

Although controversial (Waddell, 1993), recent evidence suggests that there may be a subpopulation of people who have become sensitive to chemicals and experience adverse reactions to low-level exposures to environmental chemicals (Bell, et al., 1992). Confounded in all of these groups is the role that nutrition plays in the response of the organism to exposure. Both general nutritional status and specific nutritional deficiencies (for example, protein, iron, and calcium) can significantly influence the response to a toxic substance.

It is widely accepted that during development adverse effects can result from exposure to some chemicals at lower levels than would be necessary for the average adult (Suzuki, 1980). The developing nervous system appears to be differentially sensitive to some kinds of damage (Cushner, 1981; Pearson and Dietrich, 1985; Annau and Eccles, 1986; Hill and Tennyson, 1986; Silbergeld, 1986). During the developmental period, the nervous system is actively growing and establishing intricate cellular networks. Both the blood-brain and blood-nerve barriers that will eventually protect much of the adult brain, spinal cord, and peripheral nerves are incomplete. The protective mechanisms by which the organism deals with toxic substances, such as the detoxification systems, are not fully developed. Exposure to chemicals during development can result in a range of effects. At the highest exposure, effects include death, gross structural abnormalities, or altered growth. Larger populations are generally exposed to more moderate levels resulting in more subtle functional impairments. The qualitative nature of some injuries during development may differ from those seen in the adult, such as changes in tissue volume, misplaced or misoriented neurons, or delays or acceleration of the appearance of functional or structural endpoints (Rodier, 1986). In many cases, the results of early injuries may become evident only as the nervous system matures and ages (Rodier, 1990). There are several instances in which functional alterations have resulted from exposure during the period between conception and sexual maturity (Riley and Vorhees, 1986; Vorhees, 1987).

Early exposure to relatively low levels of lead can result in reduced scores on tests of mental development (Bellinger et al., 1987; Needleman, 1990). Early gestational exposure to neurotoxicants such as cocaine can produce long-term neurobehavioral abnormalities (Anderson-Brown et al., 1990;

Hutchings et al., 1989); heavy alcohol exposure produces craniofacial abnormalities and mental retardation (Jones and Smith, 1973), while moderate levels of alcohol consumption during gestation can delay motor development (Little et al., 1989).

With aging, the level of risk for a number of health-related factors increases; it has been hypothesized that the risk for toxic perturbations to the nervous system also increases with age (Weiss, 1990). It is generally believed that with increasing age comes a decreased ability of the nervous system to respond to adverse events or to compensate for either biological, physical, or toxic effects. At the tissue and cellular level, the aging process can result in nerve cell loss, formation of neurofibrillary tangles (abnormal accumulation of certain filamentous proteins) and neuritic plaques (abnormal clusters of proteins and other substances near synapses). As cells die, the complex neuronal circuitry of the brain becomes impaired. Neurotransmitter concentrations and the enzymes involved in their synthesis may be altered. Some axons can gradually lose their myelin sheath, resulting in a slowed conduction of nerve impulses along the axon. It has been postulated that with age, not only might the nervous system become more susceptible to new insults, but the effects of previous exposures also may become evident, with a diminished capacity for compensation (Weiss, 1990). The increased incidence of multiple drug-taking in the elderly population might also lead to interactions, either drug/drug or drug/chemical, which can adversely affect the nervous system. Nutritionally, the aged experience increased incidences of both general undernutrition and deficits of specific nutrients such as iron or calcium, which might influence the response to toxic substances.

In the geriatric population, the clinical manifestation of neurodegenerative disorders may have a contributing component of past exposures to environmental chemical agents. Calne et al. (1986) hypothesized that various agents contribute to Alzheimer's disease, Parkinson's disease, or amyotrophic lateral sclerosis (ALS, motoneuron disease, or Lou Gehrig's disease) by depleting neuronal reserves to an extent that perturbations become observable in the context of the natural aging process. B-N-methylamino-L-alanine, from the seed of the false sago palm (*Cycas circinalis* L.), has been reported to induce a form of amyotrophic lateral sclerosis (Spencer et al., 1987). Alzheimer-type

syndromes have been reported in individuals occupationally exposed to organic solvents or metal vapors (Freed and Kandel, 1988). Severe cognitive dysfunction has been noted in Alzheimer's disease and aluminum intoxication (Yokel et al., 1988).

At any age, preexisting physical as well as mental disorders of the individual may play a significant role in the manifestation of a toxic response following exposure to a potentially toxic substance. Both types of disorders compromise the system in some way so that either the defense mechanisms of the organism are not able to deal with the toxic substance or are not able to repair themselves quickly. In addition to the basic altered biology, for individuals with a physical or mental disorder who are under some form of medical intervention, the combination of therapeutic drugs and toxic substances may have an interactive effect on the nervous system. For example, due to the delicate electrochemical balance of the nervous system, mental disorders may be exacerbated by exposure to a toxic substance.

2.5.2. Blood-Brain and Blood-Nerve Barriers

The bioavailability of a specific chemical to the nervous system is a function of both the target tissue and the chemical. The brain, spinal cord, and peripheral nerves are surrounded by a series of semipermeable tissues referred to as the blood-brain and blood-nerve barriers (Katzman, 1976; Peters et al., 1991). In the central nervous system, the blood-brain barrier is composed of tight junctions formed by endothelial cells and astrocytes. These tight junctions and cellular interactions forming the barrier restrict the free passage of most bloodborne substances. By doing this, they create a finely controlled extracellular environment for the nerve cells. Certain regions of the brain and nerves are directly exposed to chemicals in the blood because the barrier is not present in some areas of the nervous system. For example, it is absent in the circumventricular area, around the dorsal root ganglion in the peripheral nervous system, and around the olfactory nerve, which may allow chemicals to penetrate directly from the nasal region to the frontal cortex.

The existence of these blood-brain and blood-nerve barriers suggests that proper functioning of the nervous system is dependent on control of the substances to which nerve cells are exposed. The term "barrier," however, is somewhat of a misnomer. Although water-soluble and polar compounds enter the brain poorly, lipophilic

substances readily cross the barrier. In addition, a series of specific transport mechanisms exist through which required nutrients (hormones, amino acids, peptides, proteins, fatty acids, etc.) reach the brain (Pardridge, 1988). If toxicants are lipid soluble or if they are structurally similar to substances that are normally transported into the brain, they can achieve high concentrations in brain tissue. It has been proposed that one reason why the developing nervous system may be differentially sensitive to some toxicants is that the blood-brain barrier is less effective than in an adult. The effectiveness of the blood-brain barrier may also be changed by chemical-induced physiological events such as metabolic acidosis and nutritional deprivation.

2.5.3. Metabolism

The central nervous system has a very high metabolic rate and, unlike other organs, the brain depends almost entirely on glucose as a source of energy and raw material for the synthesis of other molecules (Damstra and Bondy, 1980). The absence of an alternative energy source makes the CNS critically dependent on an uninterrupted supply of oxygen as well as the proper functioning of enzymes that metabolize glucose. Substances can be toxic to the nervous system if they perturb neuronal metabolism. Without glucose, nerve cells usually begin to die within minutes. Despite its relatively small size, the energy demands of the brain require 14 percent of the heart's output and consumes about 18 percent of the oxygen absorbed by the lungs.

2.5.4. Limited Regenerative Ability

The nervous system has a combination of special features not found in other organ systems. It is composed of a variety of metabolically active neurons and supporting cell types that interact through a multitude of complex chemical mechanisms. Each cell type has its own functions and vulnerabilities. At the time of puberty, the system is fully developed and neurogenesis (the birth of new neurons from cell division of precursor cells called neuroblasts) ceases. This is in marked and significant contrast to almost all other tissues, where cell replacement is continual.

It is this loss of neurogenesis that limits the nervous system's ability to recover from damage and influences the plasticity of the system. Neurons are unable to regenerate following damage; therefore, they are no longer able to perform their normal functions. Toxic damage to the brain or spinal cord that results in cell loss is usually permanent.

If nerve cell loss is concentrated in one of the CNS's functional subsystems, the outcome could be debilitating; for example, a relatively small loss of neurons that use acetylcholine as their neurotransmitter may produce a profound disturbance of memory. A relatively minor insult concentrated in a subsystem that relies on dopamine as its neurotransmitter may drastically impair motor coordination. However, in response to injury, neurons are able to show considerable plasticity both during development and after maturation. Damage to the nervous system alters connectivity between the surviving neurons, permitting functional adjustments to occur to compensate for the damage. Such responsiveness may, in and of itself, have profound consequences for neurological, behavioral, and related body functions.

After damage to axons in the peripheral nerves, if the neurons are not damaged, the axons have the ability to regenerate and to attempt to reach their original target site. This is the basis, for example, of the eventual return of sensation and muscle control in a surgically reattached limb. Neurons in the CNS also have the ability to regenerate interrupted axons; however, they have a much more difficult task in reaching their original targets due to both the presence of scar tissue formed by proliferating glia and to the increased complexity of the connectivity in the CNS.

3. Methods for Assessing Human Neurotoxicity

3.1. Introduction

This chapter outlines and discusses current methods for detecting neurotoxicity in humans. In contrast to studies of neurotoxicity in animals where functional changes readily can be correlated with neuroanatomic and neurochemical alterations, there are ethical and technical barriers to the direct observation of neuronal damage in humans. Neurotoxicity in humans is most commonly measured by relatively noninvasive neurophysiologic and neurobehavioral methods that assess cognitive, affective, sensory, and motor function. The evaluation of human neurotoxicity and the relevance to risk assessment will be discussed within the context of clinical evaluation, epidemiologic/worksites studies, and human laboratory exposure studies.

3.2. Clinical Evaluation

Neurobehavioral assessment methods are used extensively in clinical neurology and neuropsychology to

evaluate patients suspected of having neurologic disease. An extensive array of examiner-administered and paper and pencil tasks are used to assess sensory, motor, cognitive, and affective functions and personality states/traits. Neurobehavioral data are synthesized with information from neurophysiologic studies, imaging techniques, medical history, etc., to derive a working diagnosis. Clinical diagnostic approaches have provided a rich conceptual framework for understanding the functions (and malfunctions) of the central and peripheral nervous systems and have formed the basis for the development of methods for measuring the behavioral expression of nervous system disorders. Human neurobehavioral toxicology has borrowed heavily from neurology and neuropsychology for concepts of nervous system impairment and functional assessment methods. Neurobehavioral toxicology has adopted the neurologic/neuropsychologic model, using adverse changes in behavioral function to assist in identifying chemically or drug-induced changes in nervous system processes.

3.2.1. Neurologic Evaluation

Assessment of neurobehavioral function by the clinical examination of a patient has long been used as a primary tool in neurologic diagnosis. The domains of cognitive function, motor function, sensation, reflexes, and cranial nerve function are a standard part of the clinical neurologic exam. Movement and gait, speech fluency and content, verbal memory, deep tendon reflexes, muscle strength, symmetry of movement and strength, ocular movements, sensory function (pressure, vibration, visual, auditory), motor coordination, and logical reasoning are only a few of the functions assessed by neurologists (Denny-Brown et al., 1982).

Trained and experienced clinicians gather these data by observation, verbal exchange, and direct examination. Neurologic exams are sensitive indicators of neurologic disease; the data have predictive value for the diagnosis of underlying nervous system disease, and the methods have been extensively validated against other diagnostic procedures (e.g., imaging, neurophysiologic testing), the course of the illness, and autopsy findings. Examination of the patient in a semistructured procedure can yield a wealth of information and insights about functional impairment and the underlying neuropathology.

3.2.2. Neuropsychological Testing

Neuropsychologists have developed quantitative methods to supplement clinical neurologic exam and laboratory data for the diagnosis of neurologic disease. Currently, two assessment batteries, the Luria-Nebraska and the Halstead-Reitan, and shorter versions are used in clinical practice. The batteries consist of subtests that quantify a wide spectrum of cognitive, motor, sensory, intellectual, affective, and personality functions. The pattern of relative performance on the subtests can be interpreted along with historical and medical data to suggest the presence or absence of neurologic disease and the possible anatomic location of any focal lesions or degeneration. Clinical interpretation of the data is enhanced by data on age-related population norms for many subtests and by the systematic observation of the patient during testing.

Several neurotoxicity assessment batteries use components of neuropsychological tests and have adapted and shortened analogs of some subtests. Tests derived from the Wechsler Adult Intelligence Scale—Revised (WAIS-R) have been used frequently to assess neurobehavioral impairment from chemical agents, and other abbreviated variations of neuropsychological battery subtests have been incorporated into neurobehavioral toxicity batteries and used in field and laboratory studies.

3.2.3. Applicability of Clinical Methods to Neurotoxicology Risk Assessment

Neurologic and neuropsychologic methods have long been employed to identify the adverse health effects of environmental workplace exposures. Peripheral neuropathies (with sensory and motor disturbances), encephalopathies, organic brain syndromes, extrapyramidal syndromes, demyelination, autonomic changes, and dementia are well-characterized consequences of acute and chronic exposure to chemical agents. The range of exposure conditions that produce clinical signs of neurotoxicity also has been defined by using these clinical methods. It is very important to make external/internal dose measurements in humans in order to determine the actual dose(s) which can cause unwanted effects.

Aspects of the clinical neurologic examination approach limit its usefulness for neurotoxicologic risk assessment. Information obtained from the neurologic exam is mostly qualitative and descriptive rather than quantitative. Estimates of the severity of functional impairment can be reliably

placed into only three or four categories (for example, mild, moderate, severe). Much of the assessment depends on the subjective judgment of the examiner; the magnitude and symmetry of muscle strength are often judged by having the patient push against the resistance of the examiner's hands. The datum is therefore the absolute and relative amount of muscle load sensed by the examiner in his or her arms.

Compared with other methods, the clinical neurologic exam may be less sensitive in detecting early neurotoxicity in peripheral sensory and motor nerves. While clinicians' judgments are equal in sensitivity to quantitative methods in assessing the amplitude of tremor, tremor frequency is poorly quantified by clinicians. Thus, important aspects of the clinical neurologic exam may be insufficiently quantified and lack sufficient sensitivity for detecting early neurobehavioral toxicity produced by environmental or workplace exposure conditions. However, a neurologic evaluation of persons with documented neurobehavioral impairment would be helpful for identifying nonchemical causes, such as diabetes and cardiovascular insufficiency.

Administration of a neuropsychological battery also requires a trained technician, and interpretation requires a trained and experienced neuropsychologist. Depending on the capabilities of the patient, 2 to 4 hours may be needed to administer a full battery; 1 hour may be needed for the shorter screening versions. These practical considerations may limit the usefulness of neuropsychological assessment in large field studies of suspected neurotoxicity.

In addition to logistical problems in administration and interpretation, neuropsychological batteries and neurologic exams share two disadvantages with respect to neurotoxicity risk assessment. First, neurologic exams and neuropsychological test batteries are designed to confirm and classify functional problems in individuals selected on the basis of signs and symptoms identified by the patient, family, or other health professionals. Their usefulness in detecting low-base rate impairment in workers or the general population may be generally thought to be limited, decreasing the usefulness of clinical assessment approaches for epidemiologic risk assessment.

Second, neurologic exams and neuropsychologic test batteries were largely developed to assess the functional correlates of the most

common forms of nervous system dysfunction: brain trauma, focal lesions, and degenerative conditions. The clinical tests were primarily validated against these neurologic disease states. There has been insufficient research to demonstrate which tests designed to assess functional expression of neurologic disease are most useful in characterizing the modes of CNS impairment produced by chemical agents and drugs. More research is needed to validate the usefulness of neuropsychologic test methods in neurotoxicology.

3.3. Current Neurotoxicity Testing Methods

3.3.1. Neurobehavioral Methods

Chemical agents directly or indirectly affect a wide range of nervous system activities. Many of these chemical actions are expressed as alterations of behavior; Anger (1990a) lists 35 neurobehavioral effects of chemical exposure that illustrate alterations in sensory, motor, cognitive, affective, and personality function. Professional judgment is important in the interpretation of data from studies using neurobehavioral methods since some endpoints can be subjective.

Dozens of tests of neurobehavioral function have been proposed or used in field or laboratory studies to assess the neurotoxicity of chemical agents. Table 3-1 lists some frequently used tests of motor, sensory, cognitive, and affective neurobehavioral function.

TABLE 3-1.—NEUROBEHAVIORAL METHODS

Neurobehavioral function	Test
Sensation	Flicker Fusion. Lanthony (color vision).
Motor/Dexterity	Pursuit Aiming. Finger Tapping. Postural Stability. Reaction Time. Santa Ana Peg Board.
Cognition	Benton Visual Retention. Continuous Performance Task. Digit-Symbol. Digit Span. Dual Tasks. Paired-Associate. Symbol-Digit Task. Wechsler Adult Intelligence Scale—Revised® (Components).

TABLE 3-1.—NEUROBEHAVIORAL METHODS—Continued

Neurobehavioral function	Test
Affect	Wechsler Memory Scale.® Profile of Mood States® (POMS).

In contrast to the individual focus in clinical evaluation, neurobehavioral tests primarily have been used to evaluate differences between groups, comparing unexposed groups with persons environmentally or occupationally exposed to a suspected neurotoxic agent. An ideal evaluation of groups for quantitative evidence of chemically induced neurobehavioral impairment would involve the assessment of a wide variety of functions, but testing all possible neurobehavioral functions that might be affected in a group of exposed workers, for example, would be impossible. Therefore, a testing strategy has been to use limited number tests that sample representative neurobehavioral functional domains such as dexterity, visual memory, and reaction time.

3.3.1.1. Test batteries.

Many field and laboratory studies have selected neurobehavioral methods according to available information about the spectrum of effects of the suspected neurotoxic agent(s). This focused strategy is useful for answering specific questions about known neurotoxins. To identify unspecified neurotoxic effects in groups of workers or to characterize the effects of less well-studied chemicals or mixtures of chemicals, several tests that sample a representative range of functional domains have been grouped into test batteries. The advantage of a standardized battery is that data from different study populations and chemical classes can be compared, and similarities in effects observed (Johnson, 1987). Standardized batteries can be categorized into investigator-administered and computer-administered types.

3.3.1.2. Investigator-administered test batteries.

The WHO-recommended Neurobehavioral Core Test Battery (NCTB) (Johnson, 1987), the Finnish Institute of Occupational Health (FIOH) (Hanninen, 1990), and the Pittsburgh Occupational Exposures Test Battery (POET) (Ryan et al., 1987) are three commonly used batteries. The NCTB is frequently used in field studies worldwide and can be fit inside a

medium-sized suitcase for transport. The NCTB consists of the following tests: simple reaction time task, digit-symbol coding task, timed motor coordination test (Santa Ana pegboard), digit span memory test, Benton Visual Retention test, pursuit aiming test, and the Profile of Mood States (POMS). Based on factor-analytic studies (Hooisma et al., 1990), these tests are believed to measure the functional domains of immediate memory, attention, dexterity/hand-eye coordination, reaction time, and mood. Long-term memory, verbal and language functions, auditory sensation, judgment, and so forth are not assessed.

3.3.1.3. Computerized test batteries.

Computerized tests and batteries have been developed for field and laboratory use. The Neurobehavioral Evaluation System (NES) (Baker et al., 1985), MicroTox (Eckerman et al., 1985), the SPES (Iregren et al., 1985), and the NCTR Operant Battery (Paule et al., 1990) are computerized systems developed for neurotoxicity assessment. Current versions of the NES, for example, consist of about 15 different neurobehavioral tests, and the battery has been used in epidemiologic studies of groups exposed to solvent, pesticide, and mercury, and in laboratory studies of NO₂, ethanol, and toluene (Letz, 1990).

Although many computerized tests appear to tap similar neurobehavioral domains as noncomputerized batteries, the visual mode of presentation, the manual mode of response, and the emphasis on speed of responding are believed to have led to significant differences in results obtained from computerized versus noncomputerized forms of similar tests. Attempts to clarify the differences between computerized and noncomputerized test batteries have met with difficulty. Although some tests are similar in each type of battery, size and duration of stimuli, presentation and response modality, number of trials, and scoring vary arbitrarily, preventing direct comparison. An example is the digit-symbol test on the NCTB and the symbol-digit test on the NES. Although almost identical in task requirements, procedural and scoring differences prevent direct comparison of the results from these two tests.

Postural stability is an aspect of integrated sensory and motor function that increasingly is being evaluated in clinical, epidemiologic, and laboratory investigations of effects of pesticides and solvents, and would be useful for assessing therapeutic drug-induced movement disorders such as

neuroleptics. Measurement of postural stability requires a computer, special software, monitor, and a force transduction platform on which the subjects must stand (Dick et al., 1990). Mechanical and capacitive field methods for assessing the amplitude and frequency of tremor also are seeing more frequent use.

An advantage of computerized testing is the standardization of test presentation, but a disadvantage is the need for delicate, expensive computers and measurement devices that require transport for field studies. Noncomputerized test batteries may be less costly to purchase and easier to transport, enhancing their desirability in field studies, but test administrators require training and small differences in test administration may affect the data.

3.3.2. Neurophysiologic Methods

With improvements in the capabilities and size of equipment, quantitative neurophysiologic measurement of sensory and motor function will be increasingly useful in human neurotoxicity evaluations. A major advantage of these methods for risk assessment is that they can be assessed in both human and animal subjects and the data can be interpreted in an homologous manner.

Electromyographic responses (EMG) and nerve conduction velocity (NCV) have been used in the assessment of peripheral nerve neurotoxicity. Some techniques require that needle electrodes be placed beneath the skin for stimulation and recording and are therefore somewhat uncomfortable for the subject. However, the methods are quantitative, provide multiple endpoints of PNS function, and have clinical relevance.

The adverse effects of solvents, pesticides, and metals have been identified with EMG/NCV neurophysiologic measures. Although not reduced as a function of duration of employment, maximum nerve conduction velocity (MCV) has been reported to vary systematically with cumulative exposure to carbon disulfide (Johnson et al., 1983), suggesting that this measure may be particularly valuable for quantitative risk assessment of some types of peripheral motor nerve toxicity.

Noninvasive neurophysiologic test methods used in neurotoxicity evaluations include the electroencephalogram (EEG), visually evoked response (VER), somatosensory evoked potential (SEP), and the brainstem auditory evoked response (BAER). The EEG is the summed electrical activity of neurons measured

with scalp electrodes; voltage and frequency are primary measures. Evoked methods employ specific eliciting stimuli applied to the sense organs to measure nervous system electrical response. Visual patterns, sounds, and cutaneous stimuli are presented to the subject, and "evoked" voltage changes in the nervous system are measured with skin electrodes.

While EEGs were developed as a tool in the neurologic diagnosis of seizure disorders and other brain diseases, dose-related EEG changes in chemically exposed (especially solvents and styrene) individuals have been noted (Seppäläinen and Harkonen, 1976). EEG measurement requires large recording devices that can be used in the laboratory or clinic, but are difficult to use in field studies. However, compact computerized recording equipment has been developed, and automated spectral analyses of EEGs have recently been applied to neurotoxicity evaluation (Piikivi and Tolonen, 1989).

In contrast to EEGs, evoked response technology is improving, and equipment, while expensive, is becoming more portable. VERs have been used to detect the sensory toxicity of solvents and carbon monoxide in human subjects, and a relationship has been suggested between BAER and blood lead levels in children exposed to lead-containing dust in the environment (Otto and Hudnell, 1990). Evoked potentials also may be conditioned, allowing the use of sensory methods to investigate associative processes.

Dose-response functions have been found with evoked methods. A curvilinear relationship was found between BAER and blood lead concentrations in children (Otto and Hudnell, 1990), and a biphasic function described visual evoked potential (VEP) latency and visual contrast sensitivity and perchloroethylene exposure concentration in a laboratory study (Altmann et al., 1991). In the latter study, the direction of the response was jointly dependent on dose and stimulus parameters. In addition, changes over time in the effect of the solvent on VEP were dose and stimulus parameter dependent.

Two important methodologic considerations are illustrated by BAER and VEP data. One is that low concentrations of some chemical agents may produce effects (shorter latencies in these examples) that could be inaccurately interpreted as facilitation rather than impairment. Changes in neuronal latencies in either direction could be a result of a neurotoxic process. The second is that the detection of neurotoxic effects is dependent on

dose-time-testing parameter interactions. A thorough understanding of the effects of testing parameters on the dose-response relationship and the time course of chemical effect will be necessary for interpreting neurotoxicity studies.

The development of neurophysiologic methods, such as evoked and conditioned potentials, for neurotoxicity risk assessment should be encouraged. These methods provide relatively unambiguous quantitative data on sensory function that may have clear implications for health, are influenced by fewer extraneous variables than are self-report and neurobehavioral performance tests, and allow relatively direct extrapolation of effects between animals and humans.

3.3.3. Neurochemical Methods

One of the major difficulties in risk assessment is estimating exposure parameters and the dose or body burden actually absorbed by the individual. In epidemiologic studies, the actual absorption and bioavailability of a chemical from an exposure are frequently unknown.

Measurement of chemical concentrations in biologic fluids or tissues is one way to measure more precisely the concentration at the site(s) of toxic effect. In epidemiologic studies, this has been possible only for chronic exposure and for acute exposure to chemicals with long biologic half-lives in the body, such as lead, other metals, and bromides. Blood lead levels show correlations with neurobehavioral impairment, but blood lead levels are representative correlates of toxicity only for relatively acute doses. In children, for example, the majority of lead-related impairment is the result of chronic, rather than acute, absorption. The cumulative amount of lead sequestered in tissues (such as deciduous teeth) may be a more representative indicator of the area under the time-concentration curve.

For chemicals with half-lives in the body too short for estimating absorbed dose, the biochemical products from the chemical or from the physiologic effects of the chemical may serve as an index of exposure. Serum enzyme concentrations (cholinesterase) and esterases in other tissues (lymphocyte target esterase) have been employed in field studies to detect pesticide exposure, while vanillylmandelic acid (product of catecholamine neurotransmitter biotransformation) and erythrocyte protoporphyrin concentrations have been used with varying success in differentiating between lead-exposed and control

workers. The addition of similar "exposure biomarker" measures to laboratory studies may allow the development of quantitative estimates of absorbed dose under various exposure conditions.

The measurement of metabolic products of neurotoxic agents may be extremely useful in risk assessment; an example comes from cancer risk assessment. Human data from the early 1970s on saturation of microsomal methylene chloride biotransformation to carbon monoxide (Stewart et al., 1972), along with subsequent animal carcinogenesis data garnered in the 1980s, provided a quantitative basis for a physiologically based pharmacokinetic model of methylene chloride cancer risk assessment (Andersen et al., 1991). The information on human CO pathway kinetics provided the homologous key that allowed extrapolation of risk from animals to humans on a comparative physiologic basis rather than using default assumptions.

3.3.4. Imaging Techniques

A number of recently developed computerized imaging techniques for evaluating brain activity and cerebral/peripheral blood flow have added valuable information to the neurologic diagnostic process. These imaging methods include thermography, positron emission tomography, passive neuromagnetic imaging (magnetoencephalography), magnetic resonance imaging, magnetic resonance spectroscopy, computerized tomography, doppler ultrasonography, and computerized EEG recording/analysis (brain electrical activity mapping). The research application of these invasive and noninvasive quantitative methods has primarily been in neurology, schizophrenia research, drug abuse, AIDS research and toxic encephalopathy (Hagstad et al., 1989). Although the equipment for brain imaging is expensive and not portable, neuroimaging techniques promise to be valuable clinical and laboratory research tools in human neurotoxicology.

3.3.5. Neuropathologic Methods

Neuropathologic examination of nervous system tissue has been used to confirm data from clinical testing and to contribute to the understanding of mechanisms of action of neurotoxicity. Peripheral nerve biopsies have confirmed chemically induced peripheral neuropathies and evaluated rates of recovery (Fullerton, 1969). Postmortem examination of nervous tissue also has elucidated the neuropathologic effects of carbon

disulfide, clioquinol, and doxorubicin (Spencer and Schaumburg, 1980).

3.3.6. Self-Report Assessment Methods

Self-report measures relevant to neurotoxicity risk assessment consist of histories of symptoms, events, behaviors, and environmental conditions. Information is obtained by face-to-face interviews, structured interviews (often conducted for diagnostic purposes), medical histories, questionnaires, and survey instruments.

Self-report instruments are the only means for measuring some symptoms and all interoceptive states, such as pain and nausea. Self-reports also are used to obtain information on behaviors and events (e.g., exposure conditions) especially when practical, legal, or ethical limitations prevent direct observation.

Subjective symptoms elucidated from self-report instruments are responsive to dose. Hanninen et al. (1979) found that subjective symptoms were positively correlated with blood lead levels in exposed workers. Subjective pain estimations are correlated with dose and type of centrally and peripherally acting analgesics, and anxiety scores on a variety of scales are responsive to the size of the anxiolytic dose.

Symptom checklists are used in epidemiologic research to identify the pattern of subjective complaints, which can be used to guide the selection of objective assessment methods. The distribution of symptoms can be correlated with indices of exposure to determine if particular symptoms are more prevalent in exposed persons (Sjogren et al., 1990).

Self-report data are notable for biases that may influence them; these biases are well known in epidemiology, clinical practice, and social science. Even in the most superficial of questions, respondents may consciously or unknowingly bias the answer to fit what they believe to be the examiner's expectations. Details of objective events or subjective states are subject to alteration; recall and reporting of remembered occurrences may be biased to fit interpretations and expectations. The socioeconomic status, gender, and affiliation of the tester also have been identified as biasing variables. Bias occurs when information is requested about behaviors, beliefs, or feelings believed by the respondent to be socially undesirable or when reinforcement contingencies (e.g., litigation) strongly favor selective reporting.

Biases in self-report data can be reduced by making the questionnaire anonymous or highly confidential;

objective data can be used to validate self-reports. Ethnographic observations, objective measurement of behavior, biologic samples, and the observations of significant others are employed to validate self-report data. Consistent descriptions of events by several persons lend credence to the reliability of the report. Many clinical interviews and self-report assessment instruments include some mechanisms for detecting self-report bias, either by looking for endorsement of improbable behaviors, or by examining the consistency of information gathered in several ways or from several sources. Concordance among biologic indices, observations, and physical examinations increases the judged validity of self-reports.

3.3.6.1. Mood scales.

Changes in mood and emotionality can be consequences of neurotoxicity. For example, case reports have identified mood changes from exposure to mercury, lead, solvents, and organophosphate insecticides. The Taylor Manifest Anxiety Scale and the Profile of Mood States (POMS) are standardized self-report assessment instruments for which there is some evidence of sensitivity to chemical insult.

The POMS, a component of the Neurobehavioral Core Test Battery, is a self-report measure that asks respondents to use a 5-point scale to rate the magnitude of 65 subjective states, such as "tense," "relaxed," "hopeless," "guilty," etc., that they have experienced within the past week. The responses are scored according to six mood factors, and a Total Mood Disturbance Score also may be calculated. Liang et al. (1990) used the POMS to evaluate lead-exposed workers (mean blood lead concentration of 41 µg/dL) from a battery plant and a control group from a fabric-weaving manufacturer. Exposed workers were significantly higher on tension, depression, anger, fatigue, and confusion scales.

Mood scales were developed to aid in assessment of psychological disorders, such as depression, and to track treatment response. In addition, mood is modulated by metabolic and endocrine variables in health and disease and can change rapidly in response to interpersonal, workplace, and environmental events. The large number of nonchemical variables and the lability of mood make inclusion of carefully selected controls essential in using affect as an endpoint in neurotoxicity research.

The validity of mood scales may be limited to the specific populations in

which the validity studies were performed. As characterizations of internal states, the meaning of the descriptors in the POMS established for one culture may not be the same as the meaning of that concept or term in other cultures or in other language systems. There may be variations in interpretation of the terms by respondents across English-speaking subcultures, perhaps as a function of education or the size of the verbal community. While these differences may not impede a global clinical interpretation, the reduction in generalizability across study populations may be sufficient to decrease the usefulness of subjective scales in quantitative neurotoxicity risk assessment.

3.3.6.2. Personality scales.

The Minnesota Multiphasic Personality Inventory (MMPI), the Cattell 16 PF, and the Eysenck Personality Inventory have occasionally been used in neurotoxicity research. Exposed and nonexposed groups have differed on several scales derived from these standardized questionnaires. The diagnostic power of the MMPI, for example, is not in the individual scales but in the pattern of scores on the 10 clinical and 3 validity scales. Because interpretation of the MMPI requires a trained diagnostician with experience in the population of interest, it is less likely to be useful in quantitative neurotoxicity assessment.

3.4. Approaches to Neurotoxicity Assessment

3.4.1. Epidemiologic Studies

Epidemiology has been defined as "the study of the distributions and determinants of disease and injuries in human populations" (Mausner and Kramer, 1985). Knowing the frequency of illness in groups and the factors that influence the distribution is the tool of epidemiology that allows the evaluation of causal inference with the goal of prevention and cure of disease. Epidemiologic studies are a means of evaluating the effects of neurotoxic substances in human populations, but such studies are limited because they must be performed shortly after exposure if the effect is acute. Most often these effects are suspected to be a result of occupational exposures due to the increased opportunity for exposure to industrial and other chemicals.

3.4.1.1. Case reports.

The first type of human study undertaken is the case report or case series, which can identify cases of a

disease and are reported by clinicians or discerned through active or passive surveillance, usually in the workplace. For example, the neurological hazards of exposure to Kepone, dimethylaminopropionitrile, and methyl-n-butyl ketone were first reported as case studies by physicians who noted an unusual cluster of diseases in persons later found to have been exposed to these chemicals (Cone et al., 1987). However, case histories where exposure involved a single neurotoxic agent, though informative, are rare in the literature; for example, farmers are exposed to a wide variety of potentially neurotoxic pesticides. Careful case histories assist in identifying common risk factors, especially when the association between the exposure and disease is strong, the mode of action of the agent is biologically plausible, and clusters occur in a limited period of time.

Case reports are inexpensive compared with other types of epidemiologic studies and can be obtained more quickly than more complex studies. They provide little information about disease frequency or population at risk, but their importance has been clearly demonstrated, particularly in accidental poisoning or acute exposure to high levels of toxicant. They remain an important source of index cases of new diseases and for surveillance in occupational settings. These studies require confirmation by additional epidemiologic research employing other study design.

3.4.1.2. Cross-sectional studies.

In cross-sectional studies or surveys, both the disease and suspected risk factors are ascertained at the same time and the findings are useful in generating hypotheses. A group of people is interviewed, examined, and tested at a single point in time to ascertain a relationship between a disease and a neurotoxic exposure. This study design does not allow the investigator to determine whether the disease or the exposure came first, rendering it less useful in estimating risk. These studies are intermediate in cost and time required to complete compared with case reports and more complex analytical studies.

3.4.1.3. Case-control (retrospective) studies.

Last (1986) defines a case-control study as one that "starts with the identification of persons with the disease (or other outcome variable) of interest, and a suitable control population (comparison, reference)

group of persons without the disease." He states that the relationship of an "attribute" to the disease is measured by comparing the diseased with the nondiseased with regard to how frequently the attribute is present in each of the groups. The cases are assembled from a population of persons with and without exposure and the comparison group is selected from the same population; the relative distribution of the potential risk factor (exposure) in both groups is evaluated by computing an odds ratio that serves as an estimate of the strength of the association between the disease and the potential risk factor. The statistical significance of the ratio is determined by calculating a p-value and is used to approximate relative risk.

The case-control approach to the study of potential neurotoxins in the environment has provided a great deal of information. In his recent text, Valciukas (1991) notes that the case-control approach is the strategy of choice when no other environmental or biological indicator of neurotoxic exposure is available. He further states: "Considering the fact that for the vast majority of neurotoxic chemical compounds, no objective biological indicators of exposure are available (or if they are, their half-life is too short to be of any practical value), the case-control paradigm is a widely accepted strategy for the assessment of toxic causation." The case-control study design, however, can be very susceptible to bias. The potential sources of bias are numerous and can be specific to a particular study, and will be discussed only briefly here. Many of these biases also can be present in cross-sectional studies. For example, recall bias or faulty recall of information by study subjects in a questionnaire-based study can distort the results of the study. Analysis of the case-comparison study design assumes that the selected cases are representative persons with the disease—either all cases with the disease or a representative sample of them have been ascertained. It further assumes that the control or comparison group is representative of the nondiseased population (or that the prevalence of the characteristic under study is the same in the control group as in general population). Failure to satisfy these assumptions may result in selection bias, but violation of assumptions does not necessarily invalidate the study results.

An additional source of bias in case-control studies is the presence of confounding variables, i.e., factors known to be associated with the exposure and causally related to the

disease under study. These must be controlled either in the design of the study by matching cases to controls on the basis of the confounding factor or in the analysis of the data by using statistical techniques such as stratification or regression. Matching requires time to identify an adequate number of potential controls to distinguish those with the proper characteristics, while statistical control of confounding requires a larger study.

The definition of exposure is critical in epidemiologic studies. In occupational settings, exposure assessment is based on the job assignment of the study subjects, but can be more precise if detailed company records allow the development of exposure profiles.

3.4.1.4. Prospective (cohort, followup) studies.

In a prospective study design, a healthy group of people is assembled and followed forward in time and observed for the development of disease. Such studies are invaluable for determining the time course for development of disease (e.g., followup studies performed in various cities on the effects of lead on child development). This approach allows the direct estimate of risks attributed to a particular exposure since disease incidence rates in the cohort are determined and allows the study of chronic effects of exposure. One major strength of the cohort design is that it allows the calculation of rates to determine the excess risk associated with an exposure. Also, biases are reduced by obtaining information before the disease develops. This approach, however, can be very time-consuming and costly.

In cohort studies information bias can be introduced when individuals provide distorted information about their health because they know their exposure status and may have been told of the expected health effects of the exposure under study.

A special type of cohort study is the retrospective cohort study in which the investigator goes back in time to select the study groups and traces them over time, often to the present. The studies usually involve specially exposed groups and have provided much assistance in estimating risks due to occupational exposures. Occupational retrospective cohort studies rely on company records of past and current employees that include information on the dates of employment, age at employment, date of departure, and whether diseased (or dead in the case of mortality studies). Workers can then be

classified by duration and degree of exposure. A retrospective cohort study was performed in which a cohort of 1,790 bricklayers and 2,601 men exposed to paint solvents was retrospectively identified and, if a disability pension had been awarded, the subjects were examined for evidence of presenile dementia. This study found a rate ratio of 3.4 for presenile dementia among the painters as compared with the bricklayers (Johnson, 1987).

3.4.2. Human Laboratory Exposure Studies

Neurotoxicity assessment has an advantage not afforded the evaluation of other toxic endpoints, such as cancer or reproductive toxicity, in that the effects of some chemicals are short in duration and reversible. Under certain circumstances, it is ethically possible to perform human laboratory exposure studies and obtain data relevant to the risk assessment process. Information from experimental human exposure studies has been used to set occupational exposure limits, mostly for organic solvents that can be inhaled.

Laboratory exposure studies have contributed to risk assessment and the setting of exposure limits for several solvents and other chemicals with acute reversible effects. These chemicals include methylene chloride, perchloroethylene, trichloroethylene, and p-xylene (Dick and Johnson, 1986).

Human exposure studies offer advantages over epidemiologic field studies. Combined with appropriate biological sampling (breath or blood), it is possible to calculate body concentrations, to examine toxicokinetics, and identify metabolites. Bioavailability, elimination, dose-related changes in metabolic pathways, individual variability, time course of effects, interactions between chemicals, interactions between chemical and environmental/biobehavioral factors (stressors, workload/respiratory rate) are some processes that can be evaluated in laboratory studies.

Other goals of laboratory studies include the indepth characterization of effects, the development of new assessment methods, and the examination of the sensitivity, specificity, and reliability of neurobehavioral assessment methods across chemical classes.

The laboratory is the most appropriate setting for the study of environmental and biobehavioral variables that affect the action of chemical agents. The effects of ambient temperature, task difficulty, the rate of ongoing behavior, conditioning variables, tolerance/

sensitization, sleep deprivation, motivation, etc., can be studied.

3.4.2.1. Methodologic aspects.

From a methodologic standpoint, human laboratory studies can be divided into two categories—between-subjects and within-subjects designs. In the former, the neurobehavioral performance of exposed volunteers is compared with that of nonexposed participants. In the latter, preexposure performance is compared with neurobehavioral function under the influence of the chemical or drug. Within-subjects designs have the advantage of requiring fewer participants, eliminating individual differences as a source of variability, and controlling for chronic mediating variables, such as caffeine use and educational achievement. A disadvantage of the within-subjects design is that neurobehavioral tests must be administered more than once. Practice on many neurobehavioral tests often leads to improved performance that may confound the effect of the chemical/drug. It is important to allow a sufficient number of test sessions in the preexposure phase of the study to allow performance on all tests to achieve a relatively stable baseline level.

3.4.2.2. Human subject selection factors.

Participants in laboratory exposure studies may be recruited from populations of persons already exposed to the chemical/drug or from naive populations. Although the use of exposed volunteers has ethical advantages, can militate against novelty effects, and allows evaluation of tolerance/sensitization, finding an accessible exposed population in reasonable proximity to the laboratory is difficult. Naive participants are more easily recruited, but may differ significantly in important characteristics from a representative sample of exposed persons. Naive volunteers are often younger, healthier, and better educated than the populations exposed environmentally, in the workplace, or pharmacotherapeutically. For example, phase I drug trial data from relatively young and healthy volunteers may not adequately predict the incidence of neurotoxic side effects in older persons with chronic health problems.

3.4.2.3. Exposure conditions and chemical classes.

Compared with workplace and environmental exposures, laboratory exposure conditions can be controlled more precisely, but exposure periods are much shorter. Generally only one or two relatively pure chemicals are studied for

several hours while the population of interest may be exposed to multiple chemicals containing impurities for months or years. Laboratory studies are therefore better at identifying and characterizing effects with acute onset and the selective effects of pure agents.

Most laboratory studies of neurobehavioral function have employed individual solvents, combinations of two solvents, or very low concentrations of chemicals released from household and office materials (volatile organic compounds). This selection is primarily because solvent effects are reversible, because there are wide margins of safety for acute effects of solvents, because solvents can be administered via inhalation methods that allow calculation of body concentrations by breath sampling methods that do not require needle sticks, because over 1 million workers may have occupational solvent exposure, and because of the extensive use of solvents in household products. Chemicals studied in the laboratory over the past 40 years have included ozone, NO₂, CO, styrene, lead, anesthetic gases, pesticides, irritants, chlorofluorocarbon compounds, and propylene glycol dinitrite. Caffeine, diazepam, and ethanol have been used in laboratory studies as positive control substances.

3.4.2.4. Test methods.

Neurobehavioral test methods may be selected according to several strategies. A test battery that examines multiple neurobehavioral functions may be more useful for screening and the initial characterization of acute effects. Selected neurobehavioral tests that measure a more limited number of functions in multiple ways may be more useful for elucidating mechanisms or validating specific effects.

3.4.2.5. Controls.

Both chemical and behavioral control procedures are valuable for examining the specificity of the effects. A concordant effect among different measures of the same neurobehavioral function (e.g., reaction time) and a lack of effect on some other measures of psychomotor function (e.g., untimed manual dexterity) would increase the confidence in a selective effect on motor speed and not on attention or on nonspecific motor function. Likewise, finding concordant effects among similar chemical or drug classes along with different effects from dissimilar classes would support the specificity of chemical effect. For example, finding that the effects of a solvent were similar to those of ethanol but not caffeine

would support the specificity of solvent effects on a given measure of neurotoxicity.

3.4.2.6. Ethical issues.

Most human exposure studies in the laboratory have been justified on the basis of data indicating that the chemical or drug exposure produces only temporary and reversible functional effects. The use of occupationally, environmentally, or therapeutically exposed populations as a source of participants also makes the risks from research exposure small relative to nonlaboratory sources of risk. Protection of human subjects is also provided by the informed consent process; the health risks (known and unknown) and benefits of the research are thoroughly explained to each participant, who may terminate participation in the study at any time.

Despite safeguards, several chemicals and drugs thought at the time of the exposure study to produce only temporary neurobehavioral effects are now (20 years later) suspected of being potential human carcinogens on the basis of animal and human data (e.g., methylene chloride, perchloroethylene). Other chemicals, however, are now thought to be less carcinogenic or otherwise less toxic in humans than once believed. Rapid advances in all areas of toxicology make it difficult to communicate, to potential subjects, reliable information about the likelihood of long-term, latent, or delayed adverse effects on health subsequent to the study. The communication of uncertainty about potential long-term effects to research participants is essential if human exposure studies are to be conducted ethically and are to continue their contributions to neurotoxicology and risk assessment.

3.5. Assessment of Developmental Neurotoxicity

3.5.1. Developmental Deficits

While adult neurotoxicology evaluates the effects of chemical exposure on relatively stable nervous system structure and function, developmental neurotoxicology addresses the special vulnerabilities of the young and the old. Neurobehavioral assessment of chemical neurotoxicity is complicated by having to measure functional impairment within a sequential progression of emergence, maturation, and gradual decline of nervous system capabilities. Methods in developmental neurotoxicity assessment must reflect the diversity of

neurobehavioral functions, from neonates to the elderly.

Exposure of pregnant women to alcohol, drugs of abuse, therapeutic drugs, nicotine, and environmental chemicals may result in the immediate or delayed appearance of neurobehavioral impairment in children (Kimmel, 1988; Nelson, 1991a). Postnatal exposure of children to chemical agents in the environment, such as lead, also may impair IQ and other indices of neurobehavioral function (Needleman et al., 1979). Neurotoxic effects may impair speech and language, attention, general intelligence, "state" regulation and responsiveness to external stimulation, learning and memory, sensory and motor skills, visuospatial processing, affect and temperament, and responsiveness to nonverbal social stimuli. Chemical neurotoxicity may be manifested as decreases in functional capabilities or delays in normative developmental progression.

Neurotoxic effects are not limited to direct exposure of the fetus or child to the chemical. Animal studies suggest that altered neurobehavioral development in offspring may result from exposure of males (Joffe and Soyka, 1981) and females to chemical substances prior to conception. In this case, altered postnatal development may reflect chemical influences on mechanisms of inheritance, copulatory behavior, nutritional status, hormonal status, or the uterine environment. In animals and humans, chemical exposure of parents may indirectly impair postnatal development through changes in milk composition, parenting behaviors, and other aspects of the environment.

In older adults the normal aging process alters the response to neurotoxicants. Both pharmacodynamic and pharmacokinetic changes may underlie altered sensitivities to the neurotoxic effects of drugs and chemicals. An example well known in geriatric medicine is the apparent increase in sensitivity of the elderly to the toxic effects of anxiolytics (Salzman, 1981). Decreases in biotransformation rate and renal elimination of parent drug and active metabolites, not related to disease processes, may partially account for the increased vulnerability (Friedel, 1978). Chronic disease states in older persons may result in decreased functional capabilities and increased vulnerability to neurotoxic effects. Chronic diseases also may prompt pharmacotherapy that may impair neurobehavioral function.

Cardiovascular, psychopharmacologic, and antineoplastic medications may

result in patterns of neurobehavioral impairment not typically seen in younger individuals.

3.5.2. Methodologic Considerations

Standardized methods are being developed for pediatric neurotoxicity assessment. Neurobehavioral functions emerge during developmental phases from neonatal stage through secondary school, and nervous system insult may be reflected not only in impairment of emergent functions, but also as delays in the appearance of new functions. Both the severity and type of deficit are affected by the dose and duration of exposure (Nelson, 1991b), and different sensitivities to chemical effects may be exhibited at different stages of nervous system development. Early episodes of exposure may produce structural damage to the nervous system that may not be developmentally expressed in behavior for several months or years.

The selection of appropriate testing methods and conditions is more important when assessing children because of shorter attention spans and increased dependence on parental and environmental supports. In addition, because of the increasing complexity of functional capabilities during early development, only a few tests appropriate for infants can be validly readministered to older children. Given the complexity of these variables, the task of devising sensitive, reliable, and valid assessment instruments or batteries for pediatric populations will be challenging.

Assessment methods in older adults must be capable of distinguishing chemical and drug effects from the effects of aging processes and chronic disease states (Crook et al., 1983). Assessment methods must be valid and reliable with repeated administration across a significant portion of the lifespan, and take into consideration the time (days, months, or years) that may intervene between exposure/insult and the expression of neurotoxicity as functional impairment. Research on nonexposed populations to develop age-appropriate normative scores for neurobehavioral functions will be important for the interpretation of assessment instruments.

Environmental exposure to neurotoxic chemicals and drugs is correlated with socioeconomic and ethnic status. Assessment methods will therefore have to be adapted to diverse ethnic, cultural, and language groups. While gender differences in early development have been noted, differential responses of males and females to neurotoxicants have been less well explored and should receive attention.

3.6. Issues in Human Neurotoxicology Test Methods

3.6.1. Risk Assessment Criteria for Neurobehavioral Test Methods

The value of human neurobehavioral test methods for quantitative risk assessment is related to the number of the following criteria that can be met:

a. Demonstrate sensitivity to the kinds of neurobehavioral impairment produced by chemicals; that is, able to detect a difference between exposed and nonexposed populations in field studies or between exposure and nonexposure periods in human laboratory research or within exposed populations over time.

b. Show specificity for neurotoxic chemical effects and not be unduly responsive to a host of other nonchemical factors, and show specificity for the neurobehavioral function believed to be measured by the test method.

c. Demonstrate adequate reliability (consistency of measurement over time) and validity (concordance with other behavioral, physiologic, biochemical, or anatomic measures of neurotoxicity).

d. Show graded amounts of neurobehavioral change as a function of exposure parameter, absorbed dose, or body burden along some ordinal or continuous metric (dose response).

e. For representative classes or subclasses of CNS/PNS-active chemicals, identify single effects or patterns of impairment across several tests or functional domains that are reasonably consistent from study to study (structure-activity).

f. Be amenable to the development of a procedurally similar counterpart that can be used to assess homologous behaviors in animals.

g. Whenever it is relevant, care must be taken to insure to the extent possible that subjects are blind to the variate of interest (Benignus, 1993).

3.6.1.1. Sensitivity.

Individual neurobehavioral tests and test batteries have detected differences between exposed and nonexposed populations in epidemiologic studies and in laboratory studies. Effects have been detected by neurobehavioral methods at concentrations thought by other kinds of evaluation not to produce neurotoxicity. Workplace exposure limits to many chemicals have been set on the basis of neurobehavioral studies. While the overall sensitivity of neurobehavioral methods is sufficient to be useful in neurotoxicology risk assessment, some methods are notably insensitive across several chemical classes while the sensitivity of other neurobehavioral tests varies according

to the spectrum of neurotoxic effects of the chemical or drug.

Sensitivity is sometimes negatively correlated with reliability; selecting for tests that show little change over time may also select for tests that are not sensitive to neurotoxic insult.

Having more control over the testing environment and using a repeated measures design may decrease variability and increase statistical power, but these tactics may introduce other problems. There is some suggestion that experience in highly structured laboratory environments with explicit stimulus conditions may reduce the sensitivity of humans and animals to the effects of drugs and chemicals, and the sensitivity of neurobehavioral measures to impairment by a chemical or drug may depend on neurobehavioral training history (Terrace, 1963; Brady and Barrett, 1986). Sensitivity may also be decreased if baseline behaviors are stable and well practiced or an escape/avoidance procedure is employed.

The systematic introduction of stimulus or response changes to induce transitional behaviors, such as in a transitional state or repeated learning paradigms, may be one way to retain the advantage of a stable baseline, have sufficient sensitivity, and avoid practice effects (Anger and Setzer, 1979).

3.6.1.2. Specificity.

There are two kinds of specificity in neurobehavioral assessment of chemical or drug neurotoxicity. Chemical specificity refers to the ability of a test to reflect chemical or drug effects and to be relatively resistant to the influence of nonchemical variables. The second type of specificity refers to the ability of a test method to measure changes in a single neurobehavioral function (e.g., dexterity) or a restricted number of functions, rather than a broad range of functions (attention, reasoning, dexterity, and vision).

The neurobehavioral expression of neurotoxic chemical or drug effects is a function of the joint interaction of ongoing nervous system processes with the chemical substance and with biopsychosocial variables that also influence nervous system activity. In laboratory exposure studies numerous environmental, behavioral, and biologic variables can influence the type or magnitude of neurotoxic effects of chemical agents and drugs (MacPhail, 1990). These variables include ambient temperature, physical workload, task difficulty, the social and tangible reward characteristics of the laboratory setting, redundancy of stimuli, the rate and form of the behavioral response, conditioning

factors, and the interoceptive stimulus properties of the chemicals.

The laboratory research participant's history and habits outside the laboratory also may affect chemical-neurobehavioral interactions by influencing the baseline level of performance on neurobehavioral tests or directly affecting the response of the CNS to the exposure. Age, gender, educational level, intellectual functioning, economic status, acute and chronic health conditions (including developmental or current neurologic conditions), alcohol/drug/tobacco effects or withdrawal, emotional status or significant life events, sleep deprivation, fatigue, and cultural factors are only a few of the variables that may affect performance in laboratory studies (Williamson, 1991; Cassitto et al., 1990).

The influence of these selection and biopsychosocial variables on the neurobehavioral effects of workplace chemicals is poorly understood, although their effects on drug-behavior interactions have been more thoroughly explored. Controlling or understanding chemical and nonchemical variables will be important for ensuring adequate specificity for risk assessment purposes.

3.6.1.3. Reliability and validity.

Reliability refers to the ability of a given test to produce closely similar results when administered more than once over a period of time or in similar populations. Reliability is meaningful only with respect to the measurement of functions that would not be expected to change significantly over the time period. Test-retest reliability coefficients are between 0.6 and 0.9 (Beaumont, 1990) for most of the tests in the NCTB. With notable exceptions, other neurobehavioral tests have similar reliabilities. Reliabilities in the 0.8 to 0.9 range are usually thought acceptable. As reliability decreases, measurement error is more likely to mask neurotoxic chemical effects.

The validity of a given neurotoxicity test relies on evidence that it adequately measures the domain of interest and is not highly correlated with tests that are believed to measure unrelated functions. These convergent and divergent aspects of validity are frequently divided into construct, content, and criterion subcategories. Construct validity refers to the ability of a given test to measure the intended function or construct (e.g., attention), content to how well the test measures the major aspects of the function, and criterion to how highly the test correlates with other tests of the same function or predicts neurotoxic impairment after similar insult.

Many neurobehavioral tests purport to measure the same or similar cognitive, sensory, or motor functions, but correlations between these tests under chemical exposure or control conditions can be disappointingly low. This is not surprising given the procedural differences that exist among neurobehavioral tests. Tests intended to measure the same function often have different presentation and response modalities (visual, verbal, manual), have differing numbers of trials or a different time limit, and have different methods for scoring the results. Many tests have such large procedural differences that direct comparison is difficult. Assessment of validity for neurobehavioral tests of specific constructs, such as attention, is further complicated in that sensory input, other cognitive processes, and motor responses are unavoidable contributors to the test result.

3.6.1.4. Dose response.

Dose in this discussion refers to the measurement of chemical or metabolite concentrations in the body and to estimations of exposure. Both exposure assessment and biologic concentrations should be measured whenever possible. Dose-response relationships have been observed both in field and laboratory studies. Two recent human solvent exposure studies used lower exposure concentration that resulted in mucosal membrane effects reported by subjects as odors or irritation (Dick et al., 1992; Hjelm et al., 1990). Neurobehavioral impairment was not detected in these studies. A review of over 50 organic solvent human exposure experiments found that neurobehavioral impairment generally occurred at mean concentrations higher than those associated with irritation, although there was often overlap among the irritant and impairment concentration ranges (Dick, 1988). Defining neurotoxic dose-response relationships in humans decreases the uncertainties of extrapolation from animal data and allows a more accurate risk assessment.

Recent human solvent exposure studies have employed low concentrations under which neurobehavioral impairment was not observed. Rather, these studies have primarily detected the effects of solvents on mucosal membranes reported by subjects as odors or irritation (Dick, unpublished observation). While these data may be relevant to setting workplace and environmental exposure limits, they can be expected to provide little information about the neurobehavioral impairment that occurs at higher concentrations. The

relationship between irritant/odor concentration-effect functions and neurobehavioral impairment concentration-effect functions is not known, but it is probably not linear. Dose-dependent mechanisms of toxic effect can be expected to complicate risk extrapolation across the dose-response range in humans.

A further complication in dose-response extrapolation is that low concentrations of chemicals may appear to improve performance as measured by neurobehavioral tests, while higher doses are more likely to impair performance. Improved performance does not necessarily indicate the absence of neurotoxicity; both increases and decreases in neurobehavioral performance may result from deleterious chemical interactions with neurons. Dose-response extrapolation is further complicated by the observation that facilitative or impairment effects within a given dosage range may occur at some parameters of the test stimulus or aspects of the response (response rate-dependent) but not at others (Altmann et al., 1991). Therefore, dose extrapolations are more difficult when there is uncertainty about the shape of the dose-response function (biphasic, linear, etc.) at the relevant test stimulus and response parameters.

The risk assessment process with animal data involves extrapolation from the effects of high doses in animals to predict the effects of chronic low-dose exposure in humans. With data from laboratory studies of humans in a risk assessment, however, the extrapolation is in the other direction, from very low-dose laboratory exposure to predict the effects of chronic exposure at higher (but still low) concentrations in the environment and workplace. Low- to high-dose extrapolation within the same species may require different assumptions and risk assessment procedures. Although high-dose human exposures have occurred in accidents, those data are primarily descriptive in nature and cannot easily be plugged into a quantitative risk extrapolation process. Low dose laboratory data may be combined with data from epidemiologic studies of persons exposed to higher concentrations.

3.6.1.5. Structure-activity.

Structure-activity relationships for well-known chemicals have largely been established by clinical methods (and animal studies) and verified by neurobehavioral and neurophysiologic testing. Although an area of active research, neurobehavioral testing of humans has not yet been able to identify reliable patterns of impairment among

chemical classes. This endeavor has been hampered by most laboratory research having been limited to the evaluation of low concentrations of solvents and a few other reversible toxicants and by the exposure uncertainties, biases, and confounding variables found in cross-sectional or cohort field studies.

3.6.2. Other Considerations in Risk Assessment

3.6.2.1. Mechanisms of action

Uncovering behavioral and neurophysiologic mechanisms of action is a potential contribution of human laboratory exposure studies to neurotoxicity risk assessment. For example, Stewart et al. (1972) demonstrated that methylene chloride was metabolized to carbon monoxide in humans, and further studies (Putz et al., 1979) found that CO production could account for some of the neurobehavioral impairment observed with that chemical. Recent human laboratory studies of solvents employed low concentrations that produced mucosal irritation and strong odor, but little neurobehavioral impairment (Dick, unpublished observation). The mechanisms of action that produce mucosal irritation and the neurotoxic mechanisms that are expressed in neurobehavioral impairment may be quite different. Data on mucosal irritation and odor may therefore provide limited information for a neurotoxicity risk assessment.

3.6.2.2. Exposure duration

A criticism of extrapolation from animal studies to human exposure conditions is that the effects of short-term exposure (months to 1-2 years) in animals may not accurately predict the effects of chronic exposure (>10 years) in humans. Laboratory studies rarely expose human subjects to solvents for more than 4-6 hours per day for 2-5 days while environmental and workplace exposures of concern involve 6-8 hours of exposure per day for years. The uncertainties of extrapolating from relatively acute exposures to predict the risks from chronic exposure will not be eliminated by using human laboratory exposure data in risk assessment.

3.6.2.3. Time-dependent effects

The acute exposures that are possible in human laboratory studies may provide little information on chronic time-dependent neurobehavioral effects. The effects of initial exposure may remain the same, decrease (tolerance), or increase (sensitization) with continued or repeated exposure to the chemical. All effects will not change in

unison; tolerance and sensitization may be observed simultaneously on different measures of neurobehavioral function. The multiple toxicodynamic effects of chemical exposure (neurobehavioral and other) seem to follow individual time courses suggestive of multiple mechanisms of action. In addition, the processes of tolerance and sensitization can be influenced by testing conditions and the nature of the behavioral task.

One also must be concerned about latent effects that do not appear for some time after a brief exposure and "silent" cumulative neurotoxic effects that are not observable in acute human studies. Latent and silent effects not only bring up the possibility of unknown risks for human subjects, but also make more difficult the extrapolation of chronic neurotoxic risks on the basis of acute exposures.

Therefore, the acute exposure conditions possible in human laboratory studies may provide us with very limited information about the long-term effects of chronic exposure.

3.6.2.4. Multiple exposures

In the environment and the workplace, persons are seldom exposed to only a single chemical. Rather, they are most often exposed to complex mixtures of chemicals, the relative concentrations of which may vary over time. For example, one farmer had more than 50 different chemical products (pesticides, herbicides, solvents, metals, gases) with nervous system effects that he used, prepared, or stored in his work shed. Chemicals used in industrial processes may also contain impurities or contaminants that may produce neurotoxic effects or alter the neurotoxicity of the more abundant chemical species. Chemical mixtures may have additive or potentiating effects not predictable from studies of single chemicals (Strong and Garruto, 1991). Human laboratory exposure studies traditionally have employed one highly purified chemical or combinations of two chemicals (usually solvents) and thus may produce a spectrum of neurotoxic effects different from environmental and occupational exposures.

Recently volatile organic compounds (VOCs) have been used in human exposure studies (Otto and Hudnell, 1991). VOCs consist of multiple volatile compounds administered at concentrations commonly found in indoor air from emissions by laminates, carpet, plastics, and other building and decorating materials. Although VOCs are thought to produce primarily mucosal irritation and odors, reports of "sick building syndrome" and

individual sensitivity to indoor air contaminants suggest that other neurobehavioral mechanisms also may be operating.

3.6.2.5. Generalizability and individual differences

The results of field studies and laboratory exposure studies are most valuable when they can be extrapolated to the general population. Studies conducted in male workers or in young, healthy volunteers may have limited applicability to women or to people in other age ranges. It therefore is important to conduct studies that include males and females of different ages and ethnic heritage. Culture-sensitive neurobehavioral test methods are being developed and validated in the United States and other countries.

While it is important to increase the generalizability of results, it is equally important to know when results cannot be generalized. Studies should be specifically directed toward identifying subsets of individuals who are more or less sensitive to neurotoxic insult or differ in mode of expression. There are many examples of individual differences that alter response to chemicals and drugs: phenylketonurics are more sensitive to dietary tyramine and persons with variants of plasma pseudocholinesterase are more affected by some neuromuscular blocking agents.

3.6.2.6. Veracity of neurobehavioral test results

In most epidemiologic and human laboratory studies, research volunteers are highly motivated to perform well on tests of neurobehavioral function. Under voluntary conditions, actual neurobehavioral performance may serve as a reasonable index of nervous system capabilities. Some studies, however, are conducted in response to complaints of symptoms thought to be related to workplace, environmental, or therapeutic exposure to chemicals and drugs. The performance of research participants with symptoms and complaints may be significantly affected (consciously or unconsciously) by monetary rewards, emotional relief, or social gains from the validation of their complaints. Under these conditions, performance may or may not accurately reflect the capabilities of the nervous system and may lead to inaccurate conclusions about the magnitude of nervous system dysfunction or about putative chemical or drug etiologies.

In addition to suboptimal performance engendered by potential reinforcers or rewards, research participants involved in disputes over suspected neurotoxic exposures or in

litigation for monetary damages are likely to be experiencing significant emotional and behavioral reactions from situational sources that can alter the outcome of neurobehavioral assessment. Anxiety, depression, sleep disturbances, fatigue, worry, obsessive thoughts, and distractibility may contribute to less than optimal performance on motor and cognitive neurobehavioral tasks, especially where speed and sustained concentration are important. Under stressful conditions, it may be extremely difficult to differentiate between neurotoxic and situational sources of observed functional impairment. Functional neurobehavioral tests are not well equipped to distinguish between impairment from neurotoxicity and from nonchemical variables. The use of functional tests in symptomatic populations requires great care in interpretation. The development of validity scales and other control procedures for assessing nonchemical influences on performance is greatly needed.

3.6.3. Cross-Species Extrapolation

Many neurobehavioral tests were developed according to constructs of human cognitive processes. The diverse measures of cognitive, sensory, and motor performance in humans are therefore not easily compared with neurobehavioral function in animals. While it may be possible to conceptually relate some animal and human neurobehavioral tests (e.g., grip strength or signal detection), many procedural differences prevent direct comparison between species.

A more direct extrapolation from animals to man might be possible if the tests were chosen on the basis of procedural similarity rather than on a conceptual basis (Anger, 1991). Stebbins and colleagues (1975) were successful in developing homologous procedures in nonhuman primates for the psychophysical evaluation of antibiotic ototoxicity. Efforts to develop comparable tests of memory and other neurobehavioral functions in animals and humans are under way (Stanton and Spear, 1990; Paule et al., 1990), and such efforts may aid in cross-species extrapolation. Other procedurally defined methods, such as Pavlovian conditioning (Solomon and Pendlebury, 1988), operant conditioning (Cory-Slechta, 1990), signal detection, and psychophysical scaling techniques (Stebbins and Coombs, 1975), could also be used to facilitate interspecies risk extrapolation. Deriving comparable neurobehavioral assessment methods in animals and humans that will allow a more straightforward extrapolation

across species is of paramount importance for neurotoxicity risk assessment.

4. Methods to Assess Animal Neurotoxicity

4.1. Introduction

4.1.1. Role of Animal Models

Determining the risk posed to human health from chemicals requires information about the potential toxicological hazards and the expected levels of exposure. Some toxicological data can be derived directly from humans. Sources of such information include accidental exposures to industrial chemicals, cases of food-related poisoning, epidemiological studies, as well as clinical investigations. While human data are available from clinical trials for therapeutics and they provide the most direct means of determining effects of potentially toxic substances, for other categories of substances, it is generally difficult, expensive, and, in some cases, unethical to develop this type of information. Quite often, the nature and extent of available human toxicological data are too incomplete to serve as the basis for an adequate assessment of potential health hazards. Furthermore, for a majority of chemical substances human toxicological data are simply not available. Consequently, for most toxicological assessments it is necessary to rely on information derived from animal models, usually rats or mice. One of the primary functions of animal studies is to predict human toxicity prior to human exposure. In some cases, species phylogenetically more similar to human, such as monkeys or baboons, are used in neurotoxicological studies.

Biologically, animals resemble humans in many ways and can serve as adequate models for toxicity studies (Russell, 1991). This is particularly true with regard to the assessment of adverse effects to the nervous system, whereby animal models provide a variety of useful information that helps minimize exposure of humans to the risk of neurotoxicity. There are many approaches to testing for neurotoxicity, including whole animal (in vivo) testing and tissue/cell culture (in vitro) testing.

At present, in vivo animal studies currently serve as the principal approach to detect and characterize neurotoxic hazard and to help identify factors affecting susceptibility to neurotoxicity. Data from animal studies are used to supplement or clarify limited information obtained from clinical or epidemiological studies in humans, as well as provide specific types of information not readily

obtainable from humans due to ethical considerations. Frequently, results from animal studies are used to guide the design of toxicological studies in humans.

In vitro tests have been proposed as a means of complementing whole animal tests, which could ultimately reduce the number of animals used in routine toxicity testing. It also has been proposed that in vitro testing, when properly developed, may be less time-consuming and more cost-effective than in vivo assessments (Goldberg and Frazier, 1989; Atterwill and Walum, 1989). By understanding the biological structures or functions affected by toxic substances in vitro, it also may be possible to predict neurotoxicological effects in the whole animal. An added advantage of in vitro testing is the growing availability of human cell lines that could be used for directly assessing potential neurotoxic effects on human tissue. The currently available strategies for in vitro testing have certain limitations, including the inability to model neurobehavioral effects such as loss of memory or sensory dysfunction or to evaluate effectively the influence of organ system interactions (e.g., neuronal, endocrinological, and immunological) on the development and expression of neurotoxicity.

In using animal models to predict neurotoxic risk in humans, it is important to understand that the biochemical and physiological mechanisms that underlie human biological processes, particularly those involving neurological and psychological functions, are very complex and are sometimes difficult, if not impossible, to model exactly in a lower species. While this caveat does not preclude extrapolating the results of animal studies to humans, it does highlight the importance of using valid animal models in well-designed experimental studies.

4.1.2. Validity of Animal Models

Whether animal tests or methods actually measure what they are intended to measure, whether the data from such tests can be obtained reliably, and whether such data can be logically extrapolated to humans are problems for most disciplines in toxicology. Various proposals have been made for the standardization and validation of methods used in neurotoxicological research. It is generally agreed that validation is an ongoing process that establishes the credibility of a test, building an increasing level of confidence in the effective utility of any model of evaluation. The credibility of a method, as it applies to testing, is

usually discussed within several different contexts, including construct validity, criterion validity, predictive validity, and detection accuracy.

Construct validity concerns the ability of a method to measure selectively a particular biological function and not other dimensions. Construct validity is frequently established empirically. For example, sensory dysfunction such as hearing loss is reported by humans exposed to some chemicals, and tests are designed to detect and quantify those changes. Such tests are designed to measure changes in auditory function, while other sensations are unaffected (Tilson, 1987; Moser, 1990).

Criterion validity refers to the ability of a method to measure a characteristic relative to some standard. For example, Horvath and Frantik (1973) noted that the significance of a test measurement as an index of an actual treatment effect should be validated relative to the effects of a defined reference substance or positive control. Furthermore, each specific test or type of effect may require an appropriate reference substance for which the given type of effect is a determining factor of the toxicity. Use of reference agents has obvious advantages in the assessment of unknown chemicals.

Predictive validity refers to the ability of a method to predict effects from an incomplete or partial data set. An animal model of neurotoxicity with good predictive validity would reliably predict neurotoxicity in humans, i.e., the animal to human extrapolation would be good. There are several examples in neurotoxicology where animal models have been developed based on neurotoxicological reports from humans. Presumably, the predictive validity of such models would enable detecting similar kinds of effects produced by uncharacterized chemicals having a similar mechanism of action.

It has been proposed (Tilson and Cabe, 1978) that the most logical approach to validate animal methods in neurotoxicology is to evaluate chemicals with and without known neurotoxicity in humans in tests designed for animals (predictive validity). By using such an approach, it is possible to generate a profile of effects characteristic of each type of neurotoxicant (criterion validity). This profile could then be used to assess the construct validity of various tests. That is, procedures assumed to measure the same neurobiological dimension should show similar effects; measures designed to detect changes in other functions should not be affected. This approach to test validation has been described as the

multitrait-multimethod process of validation (Campbell and Fiske, 1959).

Of particular importance in establishing the credibility of a method is the accuracy of detecting a treatment-related effect (Gad, 1989). Accuracy is a function of two interacting elements, specificity and sensitivity. Specificity is the ability of a test to respond positively only when the toxic endpoint of interest is present. Sensitivity is the ability to detect a change when present. This aspect depends on the inherent design of the procedure and experiment. Increasing the specificity of a test may reduce the possibility of classifying a chemical as neurotoxic when, in fact, it is not (false positive), but it may increase the probability of missing a true neurotoxicant (false negative). Increasing sensitivity of a test may reduce the possibility of false negatives, but may increase the probability of false positives.

4.1.3. Special Considerations in Animal Models

4.1.3.1. Susceptible populations.

Like most other measures of toxicological effect, neurotoxic endpoints are subject to a number of experimental variables that may affect susceptibility to the biological effects of toxicants. In this regard, genetic variation (Festing, 1991) is a particularly important issue in neurotoxicology. For example, most neurotoxicological assessments are carried out with only one or two species. This may pose problems, however, since species may differ in sensitivity to neurotoxicants. For example, nonhuman primates are more sensitive than rats (Boyce et al., 1984) or mice (Heikkila et al., 1984) to the neurodegenerative effects of MPTP, a byproduct in the illicit synthesis of a meperidine analog (Langston et al., 1983). In the assessment of delayed neuropathology produced by some cholinesterase inhibitors, it is well known that hens are much more sensitive than rodents (Cavanagh, 1954; Abou-Donia, 1981, 1983). In addition, rat strains also may be differentially sensitive to some neurotoxicants (Moser et al., 1991). Although it is preferred that more than one species be tested, the cost required for routine multispecies testing must be considered. Whenever possible, the choice of animal models should take into account differences in species with regard to pharmacodynamic, genetic composition and sensitivity to neurotoxic agents.

In addition to species, other factors such as gender of the test animal must be taken into consideration. Some toxic substances may have a greater

neurotoxicological effect in one gender (Squibb et al., 1981; Matthews et al., 1990). Thus, screening evaluations frequently require both male and female animals. Another important variable is the age of the animal (Veronesi et al., 1990). Whether a chemical produces neurotoxicity may depend on the maturational stage of the organism (Rodier, 1986). Most preliminary assessments are designed to provide information on adults, which have the greatest probability of being exposed. However, populations undergoing rapid maturation or aged individuals may be especially vulnerable to neurotoxic agents. Longitudinal studies that assess both genders at any stage of development address many of the problems associated with differentially sensitive populations.

4.1.3.2. Dosing scenario.

The dosing strategy used in experimental studies is an important variable in the development and expression of neurotoxicity (WHO, 1986). Some neurotoxicants can produce neurotoxicity following a single exposure, while others require repeated dosing. Repeated dosing represents the typical pattern of human exposure to many chemical substances. Significant differences in response may occur when an acutely toxic quantity of material is administered over different exposure periods. For some neurotoxicants the onset of neurotoxicity can occur immediately after dosing, while others may require time after exposure for the toxicity to develop. Effects of repeated exposure may result in a progressive alteration in nervous system function or structure, while latent or residual effects may be discovered only in association with age-related changes or after suitable environmental or pharmacological challenge (Zenick, 1983; MacPhail et al., 1983). To ensure adequate assessment of neurotoxicity, study designs should include multiple dosing regimens, e.g., repeated exposure, with appropriate dose-to-response intervals of testing. Conduct of neurotoxicological evaluations in studies utilizing excessively toxic doses should be avoided.

4.1.3.3. Other factors.

There are a number of other factors that should be considered in the design and interpretation of studies using animal models (WHO, 1986). Design factors include such issues as using properly trained personnel to conduct the studies, the use of appropriate numbers of animals per group to achieve reliable statistical significance, and controlling the time-of-day

variability. Time of testing relative to exposure is also important for assessing neurotoxic endpoints such as behavior, and experiments should be designed to generate a time course of effects, including recovery of function, if any. Housing is an important environmental design factor, because animals housed individually and animals housed in groups can respond differently to toxic agents. Temperature, as an experimental variable, may also affect the outcome of neurotoxicological studies. The responsiveness to some chemicals (e.g., triethyltin, methamphetamine) varies with ambient temperature (Dyer and Howell, 1982; Bowyer et al., 1992). Some neurobiological endpoints, such as sensory evoked potentials, can be influenced by the endogenous temperature of the animal (Dyer, 1987). Therefore, changes in body temperature, whether due to fluctuations in ambient temperature or to some chemically induced effect such as inhibition of sweating, can confound the interpretation of measures such as evoked responses unless proper controls are included in the experimental design.

Because a variety of other physiological changes can influence neuronal functions, it is important to recognize that chemical-related neurotoxicity could result from treatment-induced physiological changes, such as altered nutritional state (WHO, 1986). As part of a neurotoxicological profile, correlative measures, such as relative and absolute organ weights, food and water consumption, and body weight and weight gain, may be signs of physiological change associated with systemic toxicity and may be useful in determining the relative contribution of general toxicity.

4.1.3.4. Statistical considerations.

Experimental designs for neurotoxicological studies are frequently complex, with two or more major variables (e.g., gender, time of testing) varying in any single experiment. In addition, such studies typically generate varying types of data, including continuous, dichotomous, and rank-order data. Knowledge and experience in experimental design and statistical analyses are important. There are several key statistical concepts that should be understood in neurotoxicological studies (WHO, 1986; Gad, 1989). The power, or probability, of a study to detect a true effect is dependent on the size of the study group, the frequency of the outcome variable in the general population, and the magnitude of effect to be identified. Statistical evaluation of a treatment-

related effect involves the consideration of two factors or types of errors to be avoided. A Type I error refers to the attribution of an exposure-related neurotoxicological effect when none has occurred (false positive), while a Type II error refers to the failure to attribute an effect when an exposure-related effect has actually occurred (false negative). In general, the probability of a Type I error should not exceed 5 percent and the probability of a Type II error should not exceed 20 percent. Power is defined as one minus the probability of a Type II error.

Determination of power also requires knowledge of the difference in magnitude of outcome measures observed between exposed and control groups and the variability of the outcome measure among subjects. The sample size required to achieve a given level of statistical power increases as variability increases or the difference between groups decreases.

Continuous data (i.e., magnitude, rate, amplitude), if found to be normally distributed, can be analyzed with a general linear model using a grouping factor of dose and, if necessary, repeated measures across time. Post hoc comparisons between control and other treatment groups can be made following tests for overall significance. In the case of multiple endpoints within a series of evaluations, correction for multiple observations (e.g., Bonferroni's) might be necessary.

Descriptive data (categorical) and rank data can be analyzed using standard nonparametric techniques. In some cases, if it is believed that the data fit the linear model, the categorical data modeling procedure can be used for weighted least-squares estimation of parameters for a wide range of general linear models, including repeated measures analyses. The weighted least-squares approach to categorical and rank data allows computation of statistics for testing the significance of sources of variation as reflected by the model.

4.2. Tiered Testing in Neurotoxicology

The utility of tiered testing as an efficient and cost-effective approach to evaluate chemical toxicity, including neurotoxicity, has been recognized (NRC, 1975). Briefly, first-tier tests are designed to determine the presence or absence of neurotoxicity, while second-tier tests characterize the neurotoxic effect (NRC, 1992). There are at least two aspects of tiered testing, one involving the type of test used (Tilson, 1990a) and the other involving the dosing regimen (Goldberg and Frazier, 1989).

4.2.1. Type of Test

Tests designed to measure the presence or absence of an effect are usually different from those used to assess the degree of toxicity or the lowest exposure level required to produce an effect (Tilson, 1990a). Screening procedures are first-tier tests that typically permit the testing of many groups of animals. Such procedures may not require extensive resources and are usually simple to perform. However, these techniques may be labor intensive, provide subjective measures, yield semiquantitative data, and may not be as sensitive to subtle effects as those designed to characterize neurotoxic effects or second-tier tests. Specialized tests are usually more sensitive and employed in studies concerning mechanisms of action or the estimation of the lowest effective dose. Such testing procedures are usually referred to as secondary tests and may require special equipment and more extensive resources. Secondary tests are usually quantitative and yield graded or continuous data amenable to routine parametric statistical analyses.

Testing at the first tier is used to determine if a chemical might produce neurotoxicity following exposure, i.e., hazard detection. In this case, there may be little existing information concerning the neurotoxic potential of an agent. Examples of first-tier tests include functional observational batteries (FOB), including an evaluation of motor activity and routine neurohistopathology. For some chemicals or types of chemicals, there may be a specific interest in screening for a particular presumed mechanism of toxicity (e.g., inhibition of cholinesterase or neurotoxic esterase) or neurobiological response (e.g., a site-specific neuronal degeneration). In these cases, specific neurochemical or neuropathological endpoints can be used in conjunction with first-tier tests. It is desirable that tests selected for use in hazard detection provide a suitable level of sensitivity using the smallest number of animals necessary.

A decision to test at the next tier is based on data suggesting that an agent produces neurotoxicity. The information used to make a decision to test a chemical at the secondary level can come from a variety of sources, including neurotoxicological data already in the literature, structure-activity relationships, data from first-tier testing, or following reports of specific neurotoxic effects in humans exposed to the agent. Testing at the secondary level includes detailed neuropathological evaluation as well as specific behavioral

tests, e.g., procedures to assess learning and memory, or sensory function. Tests at the second tier usually measure the most sensitive endpoints of neurotoxicity, and are the most suitable for determining the no observable adverse effect level or benchmark dose. At this stage of testing, the use of a second species is considered to address the issue of cross-species extrapolation. At the present time, tiered testing approaches in neurotoxicology rely heavily on functional endpoints. It is possible that future testing protocols will employ a different strategy as more information concerning neurotoxic mechanisms of action become available and biologically based dose-response models are developed.

4.2.2. Dosing Regimen

Goldberg and Frazier (1989) have indicated that first-tier evaluations identify effects of substances following acute or repeated exposure over a wide range of doses. Measures are simple, focused on detection of effects, and results are used to help establish parameters for the second tier of testing. The subsequent stage(s) of tier testing are designed to characterize more fully the toxicity of repeated dosing. In this case, animals are exposed repeatedly or continuously to define the scope of toxicity, including latent or delayed effects, development of tolerance, and the reversibility of adverse effects. The subsequent stage(s) of testing also provide information about specific effects or study mechanisms of neurotoxicity. This tier uses methods appropriate to characterize the effects observed in the first tier of testing.

4.3. Endpoints of Neurotoxicity

4.3.1. Introduction

As applied to the safety assessment of chemical substances, neurotoxicity is any adverse change in the development, structure, or function of the central and peripheral nervous system following exposure to a chemical agent (Tilson, 1990b). Measures used in animal neurotoxicological studies are designed to assess these changes. Neurotoxicity can be described at multiple levels of organization, including chemical, anatomical, physiological, or behavioral levels. At the chemical level, for example, a neurotoxic substance might inhibit protein or transmitter synthesis, alter the flow of ions across cellular membranes, or prevent release of neurotransmitter from nerve terminals. Anatomical changes may include destruction of the neuron, axon, or myelin sheath. At the physiological level, neuronal responsiveness to

stimulation might be enhanced by a decrease of inhibitory thresholds in the nervous system. Chemical-induced effects at the behavioral level can involve a variety of alterations in motor, sensory, or cognitive function, including increases or decreases in frequency or accuracy of responding. Although behavioral and neurophysiological endpoints may be very sensitive indicators of neurotoxicity, they can be influenced by other factors. The uncertainties associated with data from functional endpoints can be reduced if interpreted within the context of other neurotoxicological measures (neurochemical or neuropathological) and systemic toxicity endpoints, particularly if such measures are taken concurrently. Behavioral effects that reflect an indirect effect secondary to systemic toxicities may also be considered adverse. Table 4-1 provides examples of potential endpoints of neurotoxicity at the behavioral, physiological, chemical, and structural levels.

TABLE 4-1.—EXAMPLES OF POTENTIAL ENDPOINTS OF NEUROTOXICITY

Behavioral Endpoints:

- Absence or altered occurrence, magnitude, or latency of sensorimotor reflex
- Altered magnitude of neurological measurements, such as grip strength or hindlimb splay
- Increases or decreases in motor activity
- Changes in rate or temporal patterning of schedule-controlled behavior
- Changes in motor coordination, weakness, paralysis, abnormal movement or posture, tremor, ongoing performance
- Changes in touch, sight, sound, taste, or smell sensations
- Changes in learning and memory
- Occurrence of seizures
- Altered temporal development of behaviors or reflex responses
- Autonomic signs

Neurophysiological Endpoints:

- Change in velocity, amplitude, or refractory period of nerve conduction
- Change in latency or amplitude of sensory-evoked potential
- Change in EEG pattern or power spectrum

Neurochemical Endpoints:

- Alterations in synthesis, release, uptake, degradation of neurotransmitters
- Alterations in second messenger associated signal transduction
- Alterations in membrane-bound enzymes regulating neuronal activity
- Decreases in brain AChE
- Inhibition of NTE
- Altered developmental patterns of neurochemical systems
- Altered proteins (c fos, substance P)

Structural Endpoints:

TABLE 4-1.—EXAMPLES OF POTENTIAL ENDPOINTS OF NEUROTOXICITY—Continued

Accumulation, proliferation, or rearrangement of structural elements
Breakdown of cells
GFAP increases (adult)
Gross changes in morphology, including brain weight
Discoloration of nerve tissue
Hemorrhage in nerve tissue

4.3.2. Behavioral Endpoints

Neurotoxicants produce a wide array of functional deficits, including motor, sensory, and learning or memory dysfunction (WHO, 1986; Tilson and Mitchell, 1984). Many procedures have been devised to assess overt as well as relatively subtle changes in those functions; hence their applicability to the detection of neurotoxicity and to hazard characterization. Many of the behavioral tests have been developed

and validated with well-characterized neurotoxicants. Behavioral tests and agents that affect them have been reviewed recently (WHO, 1986; Cory-Slechta, 1989). Examples of such tests, the nervous system function being measured, and neurotoxicants known to affect these measures are listed in Table 4-2.

TABLE 4-2. EXAMPLES OF SPECIALIZED TESTS TO MEASURE NEUROTOXICITY

Function	Procedure	Representative agents
Neuromuscular:		
Weakness	Grip strength; swimming endurance; suspension from rod; discriminative motor function; hindlimb splay.	n-hexane, methyl butylketone, carbaryl.
Incoordination	Rotorod, gait measurements	3-acetylpyridine, ethanol.
Tremor	Rating scale, spectral analysis	Chlordecone, Type I pyrethroids, DDT.
Myoclonia, spasms	Rating scale, spectral analysis	DDT, Type II pyrethroids.
Sensory:		
Auditory	Discriminated conditioning Reflex modification	Toluene, trimethyltin.
Visual toxicity	Discriminated conditioning	Methyl mercury.
Somatosensory toxicity.	Discriminated conditioning	Acrylamide.
Pain sensitivity	Discriminated conditioning (titration); functional observational battery	Parathion.
Olfactory toxicity	Discriminated conditioning	3-methylindole methylbromide.
Learning/Memory:		
Habituation	Startle reflex	Diisopropyl-fluorophosphate (DFP).
Classical conditioning	Nictitating membrane	Aluminum.
	Conditioned flavor aversion	Carbaryl.
	Passive avoidance	Trimethyltin, IDPN.
	Olfactory conditioning	Neonatal trimethyltin.
	One-way avoidance	Chlordecone.
Operant or instrumental conditioning.		
	Two-way avoidance	Neonatal lead.
	Y-maze avoidance	Hypervitaminosis A.
	Biel water maze	Styrene.
	Morris water maze	DFP.
	Radial arm maze	Trimethyltin.
	Delayed matching to sample	DFP.
	Repeated acquisition	Carbaryl.
	Visual discrimination learning	Lead.

4.3.2.1. Functional observational batteries.

Functional observational batteries are first-tier tests designed to detect and quantify major overt behavioral, physiological, and other neurotoxic effects (Moser, 1989). A number of

batteries have been used (Tilson and Moser, 1992), each consisting of tests generally intended to evaluate various aspects of sensorimotor function. Most FOB are similar to clinical neurological examinations that rate presence or absence and, in some cases, the relative degree of neurological signs. A typical

FOB, as summarized in Table 4-3, evaluates several functional domains, including neuromuscular (i.e., weakness, incoordination, gait, and tremor), sensory (i.e., audition, vision, and somatosensory), and autonomic (i.e., pupil response and salivation) function.

TABLE 4-3.—SUMMARY OF MEASURES IN THE FUNCTIONAL OBSERVATIONAL BATTERY AND THE TYPE OF DATA PRODUCED BY EACH

Home cage and open field	Manipulative	Physiologic
Posture (D)	Ease of removal (R)	Body temperature (I)
Convulsions, tremors (D)	Handling reactivity (R)	Body weight (I)
Palpebral closure (R)		
Lacrimation (R)	Approach response (R)	
Piloerection (Q)	Click response (R)	
Salivation (R)	Touch response (R)	
Vocalizations (Q)	Tail pinch response (R)	
Rearing (C)	Righting reflex (R)	

TABLE 4-3.—SUMMARY OF MEASURES IN THE FUNCTIONAL OBSERVATIONAL BATTERY AND THE TYPE OF DATA PRODUCED BY EACH—Continued

Urination (C)	Landing foot splay (I)
Defecation (C)	Forelimb grip strength (I)
Gait (D, R)	Hindlimb grip strength (I)
Arousal (R)	Pupil response (Q)
Mobility (R)	
Stereotypy (D)	
Bizarre behavior (D)	

D = descriptive data; R = rank order data; Q = quantal data;
I = interval data; C = count data

The major advantages of FOB tests are that they can be administered within the context of other ongoing toxicological tests and provide some indication of the possible neurological alterations produced by exposure. Potential problems include insufficient interobserver reliability, difficulty in defining certain endpoints, and the tendency toward observer bias. The latter can be controlled by using observers unaware of the actual treatment of the subjects. Some FOB tests may not be very sensitive to agent-induced sensory loss (i.e., vision, audition) or alterations in cognitive or integrative processes such as learning and memory. FOB data may be used to trigger experiments performed at the next tier of testing.

FOB data may be interval, ordinal, or continuous (Creason, 1989). The relevance of statistically significant test results from an FOB is judged according to the number of signs affected, the dose(s) at which neurotoxic signs are observed, and the nature, severity, and persistence of the effects. Data from the FOB may provide presumptive evidence of adverse effects and neurotoxicity. If only a few unrelated measures in the FOB are affected or the effects are unrelated to dose, there is less concern about neurotoxic potentials of a chemical. If dose is associated with other overt signs of toxicity, including systemic toxicity, large decreases in body weight, or debilitation, the data must be interpreted carefully. In cases where several related measures in a battery of tests are affected and the effects appear to be dose dependent, the level of concern about the potential of a chemical is higher.

4.3.2.2. Motor activity.

Movement within a defined environment is a naturally occurring response and can be affected by environmental agents. Motor activity represents a broad class of behaviors involving coordinated participation of sensory, motor, and integrative

processes. Motor activity measurements are noninvasive and can be used to evaluate the effects of acute and repeated exposure to chemicals (MacPhail et al., 1989). Motor activity measurements have also been used in humans to evaluate disease states, including disorders of the nervous system (Goldstein and Stein, 1985). The assessment of motor activity is often included in first-tier evaluations, either as part of the FOB or as a separate quantitated measurement.

There are many different types of activity measurement devices, differing in size, shape, and method of movement detection (MacPhail et al., 1989). Because of the accuracy and ease of calibration, devices with photocells are widely used. In general, situating the apparatus to minimize extraneous noise, movements, or lights usually requires that the recording devices be placed in light- and sound-attenuating chambers during the testing period. A number of different factors, including age, gender, and time of day, can affect motor activity, and should be controlled or counterbalanced. Different strains of animals may have significantly different basal levels of activity, making comparisons across studies difficult. A major factor in activity studies is the duration of the testing session. Motor activity levels are generally highest at the beginning of the session and decrease to a low level throughout the session. The rate of decline during the test session is frequently termed "habituation."

Motor activity measurements are typically included as part of a battery of tests to detect or characterize neurotoxicity. Agent-induced alterations in motor activity associated with overt signs of toxicity (e.g., loss of body weight, systemic toxicity) or occurring in non-dose-related fashion are of less concern than changes that are dose dependent, related to structural or other functional changes in the nervous system, or occur in the absence of life-

threatening toxicity and are generally convincing evidence of neurotoxicity.

4.3.2.3. Neuromotor function.

Motor dysfunction is a common neurotoxic effect, and many different types of tests have been devised to measure time- and dose-dependent effects. Anger (1984) reported 14 motor effects of 89 substances, which could be classified into four categories: weakness, incoordination, tremor, and myoclonia or spasms. Chemical-induced changes in motor function can be determined with relatively simple techniques such as the FOB. More specialized tests to assess weakness include measures of grip strength, swimming endurance, suspension from a hanging rod, discriminative motor function, and hindlimb splay. Rotarod and gait assessments measure incoordination, while rating scales and spectral analysis techniques quantify tremor and other abnormal movements (Tilson and Mitchell, 1984).

An example of a second-tier procedure to assess motor function has been described by Newland (1988), who trained squirrel monkeys to hold a bar within specified limits (i.e., displacement) to receive positive reinforcement. The bar was also attached to a rotary device, which allowed measurement of chemical-induced tremor. Spectral analysis was used to characterize the tremor, which was found to be similar to that seen in humans exposed to neurotoxicants or with such neurologic diseases as Parkinson's disease.

Incoordination and performance changes can be assessed with procedures that measure chemical-induced alterations in force (Fowler, 1987). The accuracy of performance may reflect neuromotor function and is sensitive to the debilitating effects of many psychoactive drugs (Walker et al., 1981; Newland, 1988). Gait, an index of coordination, has been measured in rats under standardized conditions and can be a sensitive indication of specific

damage to the basal ganglia and motor cortex (Hruska et al., 1979) as well as damage to the spinal cord and peripheral nervous system.

Procedures to characterize chemical-induced motor dysfunction have been used extensively in neurotoxicology. Most require preexposure training (including alterations of motivational state) of experimental animals, but such tests might be useful, in as much as similar procedures are often used in assessing humans.

4.3.2.4. Sensory function.

Alterations in sensory processes (e.g., paresthesias and visual or auditory impairments) are frequently reported signs or symptoms in humans exposed to toxicants (Anger, 1984). Several approaches have been devised to measure sensory deficits. Data from tests of sensory function must be interpreted within the context of changes in body weight, body temperature, and other physiological endpoints. Furthermore, many tests assess the behavioral response of an animal to a specific sensory stimulus; such responses are usually motor movements that could be directly affected by chemical exposure. Thus, care must be taken to determine whether proper controls were included to eliminate the possibility that changes in response to a sensory stimulus may have been related to agent-induced motor dysfunction.

Several first-tier testing procedures have been devised to screen for overt sensory deficits. Many rely on orientation or the response of an animal to a stimulus. Such tests are usually included in the FOB used in screening (e.g., tail-pinch or click responses). Responses are usually recorded as being either present, absent, or changed in magnitude (Moser, 1989; O'Donoghue, 1989). Screening tests for sensory deficits are typically not suitable to characterize chemical-induced changes in acuity or fields of perception. The characterization of sensory deficits usually necessitates psychophysical methods that study the relationship between the physical dimensions of a stimulus and the behavioral response it generates (Maurissen, 1988).

One second-tier approach to the characterization of sensory function involves the use of reflex-modification techniques (Crofton, 1990). Chemical-induced changes in the stimulus frequency or threshold required to inhibit a reflex are taken as possible changes in sensory function. Prepulse inhibition has been used only recently in neurotoxicology (Fechter and Young, 1983) and can be used to assess sensory

function in humans as well as in experimental animals.

Various behavioral procedures require that a learned response occur only in the presence of a specific stimulus (i.e., discriminated or conditioned responding). Chemical-induced changes in sensory function are determined by altering the physical characteristics of the stimulus (e.g., magnitude or frequency) and measuring the alteration in response rate or accuracy. In an example of the use of a discriminated conditional response to assess chemical-induced sensory dysfunction, Maurissen et al. (1983) trained monkeys to respond to the presence of a vibratory or electric stimulus applied to the fingertip. Repeated dosing with acrylamide produced a persistent decrease in vibration sensitivity; sensitivity to electric stimulation was unimpaired. That pattern of sensory dysfunction corresponded well to known sensory deficits in humans. Discriminated conditional response procedures have been used to assess the ototoxicity produced by toluene (Pryor et al., 1983) and the visual toxicity produced by methylmercury (Merigan, 1979).

Procedures to characterize chemical-induced sensory dysfunction have been used often in neurotoxicology. As in the case of most procedures designed to characterize nervous system dysfunction, training and motivational factors can be confounding factors. Many tests designed to assess sensory function for laboratory animals can also be applied with some adaptation to humans.

4.3.2.5. Learning and memory.

Learning and memory disorders are neurotoxic effects of particular importance. Impairment of memory is reported fairly often by adult humans as a consequence of toxic exposure. Behavioral deficits in children have been caused by lead exposure (Smith et al., 1989), and it is hypothesized (Calne et al., 1986) that chronic low-level exposure to toxic agents may have a role in the pathogenesis of senile dementia.

Learning can be defined as an enduring change in the mechanisms of behavior that results from experience with environmental events (Domjan and Burkhard, 1986). Memory is a change that can be either short-lasting or long-lasting (Eckerman and Bushnell, 1992). Alterations in learning and memory must be inferred from changes in behavior. However, changes in learning and memory must be separated from other changes in behavior that do not involve cognitive or associative processes (e.g., motor function, sensory capabilities, and motivational factors),

and an apparent toxicant-induced change in learning or memory should be demonstrated over a range of stimuli and conditions. Before it is concluded that a toxicant alters learning and memory, effects should be confirmed in a second learning procedure. It is well known that lesions in the brain can inhibit learning. It is also known that some brain lesions can facilitate some types of learning by removing behavioral tendencies (e.g., inhibitory responses due to stress) that moderate the rate of learning under normal circumstances. A discussion of learning procedures and examples of chemicals that can affect learning and memory have appeared in recent reviews (Heise, 1984; WHO, 1986; Peele and Vincent, 1989).

One simple index of learning and memory, which can be measured as a first-tier endpoint, is habituation. Habituation is defined as a gradual decrease in the magnitude or frequency of a response after repeated presentations of a stimulus. A toxicant can affect habituation by increasing or decreasing the number of stimulus presentations needed to produce response decrements (Overstreet, 1977). Although habituation is a very simple form of learning, it can also be perturbed by a number of chemical effects not related to learning.

A more complicated approach to studying the effects of a chemical on learning and memory involves the pairing of a novel stimulus with a second stimulus that produces a known, observable, and quantifiable response (i.e., classical "Pavlovian" conditioning). The novel stimulus is known as the conditioned stimulus, and the second, eliciting stimulus is the unconditioned stimulus. With repeated pairings of the two stimuli, the conditioned stimulus comes to elicit a response similar to the response elicited by the unconditioned stimulus. The procedure has been used in behavioral pharmacology and, to a lesser extent, in neurotoxicology. Neurotoxicants that interfere with learning and memory would alter the number of presentations of the pair of stimuli required to produce conditioning or learning. Memory would be tested by determining how long after the last presentation of the two stimuli the conditioned stimulus would still elicit a response (Yokel, 1983). Other classically conditioned responses known to be affected by psychoactive or neurotoxic agents are conditioned taste aversion (Riley and Tuck, 1985) and conditioned suppression (Chiba and Ando, 1976).

Second-tier procedures to assess learning or memory typically involve

the pairing of a response with a stimulus that increases the probability of future response through reinforcement. Response rate can be increased by using positive reinforcement or removing negative reinforcement. Learning is usually assessed by determining the number of presentations or trials needed to produce a defined frequency of response. Memory can be defined specifically as the maintenance of a stated frequency of response after initial training. Neurotoxicants may adversely affect learning by increasing or decreasing the number of presentations required to achieve the designated criterion. Decrements in memory may be indicated by a decrease in the probability or frequency of a response at some time after initial training. Toxicant-induced changes in learning and memory should be interpreted within the context of possible toxicant-induced changes in sensory, motor, and motivational factors. Examples of instrumental learning procedures used in neurotoxicology are repeated acquisition (Schrot et al., 1984), passive and active avoidance, Y-maze avoidance, spatial mazes (radial-arm maze), and delayed matching to sample (Heise, 1984; WHO, 1986; Tilson and Mitchell, 1984).

4.3.2.6. Schedule-controlled behavior.

Another type of second-tier procedure is schedule-controlled operant behavior (SCOB), which involves the maintenance of behavior (performance) by response-dependent reinforcement (Rice, 1988). Different patterns of behavior and response rates are controlled by the relationship between response and later reinforcement. SCOB affords a measure of learned behavior and with appropriate experimental design may be useful for studying chemical-induced effects on motor, sensory, and cognitive function.

The primary endpoints for evaluation are agent-induced changes in response rate or frequency and the temporal pattern of responding. Response rate is usually related to an objective response, such as lever press or key peck, and differs according to the schedule of reinforcement. Response rates are expressed per unit of time. For some classes of chemicals, the direction of an effect on response rate can differ between low and high doses. Agent-induced changes in temporal pattern of responding can occur independently of changes in the rate and require analysis of the distribution of responses relative to reinforcement schedule.

SCOB has been used to study the effects of psychoactive drugs on

behavior and is sensitive to many neurotoxicants, including methylmercury, solvents, pesticides, acrylamides, carbon monoxide, and organic and inorganic lead (Paule and McMillan, 1984; MacPhail 1985; Cory-Slechta, 1989; Rice, 1988). The experimental animal often serves as its own control, and the procedure provides an opportunity to study a few animals extensively over a relatively long period. SCOB typically requires motivational procedures, such as food deprivation, and training sessions are usually required to establish a stable baseline of responding. Because of its sensitivity to neuroactive chemicals, SCOB has great potential for use in second-tier assessments.

4.3.3. Neurophysiological Endpoints of Neurotoxicity

Neurophysiological studies are those that assess function either directly through measurements of the electrical activity of the nervous system (electrophysiology) or indirectly through measurements of peripheral organ functions controlled or modulated by the nervous system (general physiology) (Dyer, 1987). When performed properly, neurophysiological techniques provide information on the integrity of defined portions of the nervous system. Many of the endpoints used in animals have also been used in humans to determine chemical-induced alterations in neurophysiological function.

The term "electrophysiology" refers to the set of neurophysiological procedures that study neural function through the direct measurement of the electrical activity generated by the nervous system (Dyer, 1987). A variety of electrophysiological procedures are available for application to neurotoxicological problems, which range in scale from procedures that employ microelectrodes to study the function of single nerve cells or restricted portions of them, to procedures that employ macroelectrodes to perform simultaneous recordings of the summed activity of many cells. The latter types of procedures have historically been used in studies to detect or characterize the potential neurotoxicity of agents of regulatory interest. Several macroelectrode procedures are discussed below.

4.3.3.1. Nerve conduction studies.

Nerve conduction studies are generally performed on peripheral nerves and can be useful in investigations of possible peripheral neuropathy. Most peripheral nerves contain mixtures of both individual

sensory and motor nerve fibers, which may or may not be differentially sensitive to neurotoxicants. It is possible to distinguish sensory from motor effects in peripheral nerve studies by measuring activity in purely sensory nerves such as the sural to study sensory effects or by measuring the muscle response evoked by nerve stimulation to measure motor effects. While a number of endpoints can be recorded, the most commonly used variables are (1) Nerve conduction velocity, and (2) response amplitude. In well-controlled studies, decreases in nerve conduction velocity typically are evidence of neurotoxicity (Dyer, 1987). While a decrease in nerve conduction velocity is a reliable measure of demyelination, it frequently occurs rather late in the course of axonal degradation because normal conduction velocity may be maintained for some time in the face of axonal degeneration. For this reason, a measurement of normal nerve conduction velocity does not necessarily rule out peripheral axonal degeneration if other signs of peripheral nerve dysfunction are present. Increases in conduction velocity of adult organisms following treatment with neurotoxic compounds, in the absence of hypothermia, are atypical responses and may, in fact, reflect experimental or statistical errors. Decreases in response amplitude reflect a loss of active nerve fibers, and may occur prior to decreases in conduction velocity in the course of peripheral neuropathy. Hence changes in response amplitude may be more sensitive measurements of axonal degeneration than conduction velocity. Measurements of response amplitude, however, are more variable and require careful experimental techniques, a larger sample size, and greater statistical power than measurements of velocity to detect changes. Alterations in peripheral nerve function are associated with abnormal peripheral sensations such as numbness, tingling, or burning or with motor impairments such as weakness. Examples of compounds that alter peripheral nerve function in humans or experimental animals at some level of exposure include acrylamide, carbon disulfide, hexacarbonyl, lead, and some organophosphates.

4.3.3.2. Sensory evoked potentials.

Sensory evoked potentials are electrophysiological procedures that involve measuring the response elicited by the presentation of a defined sensory stimulus such as a tone, a light, or a brief electrical pulse to the skin. Sensory evoked potentials reflect sensory function, and can be used to

investigate visual, auditory, or somatosensory (body sensation) systems (Rebert, 1983; Mattsson and Albee, 1988). The data are in the form of a voltage record over time, which can be quantified in several ways. Commonly, the positive and negative voltage peaks are identified and measured as to their latency (time from stimulus onset) and amplitude (voltage).

Changes in peak amplitudes or equivalent measures reflect changes in the magnitude of the neural population that is responsive to stimulation. Both increases and decreases in amplitude are possible following exposure to neurotoxicants because (1) The brain normally operates in a careful balance between excitatory and inhibitory systems, and disruption of this balance can produce either positive or negative shifts in the voltages recorded in evoked potential experiments, and (2) excitatory or inhibitory neural activity is translated into a positive or negative deflection in the sensory evoked potential depending on the physical orientation of the electrode with respect to the tissue generating the response, which is frequently unknown. Within any given sensory system, the neural circuits that generate the different evoked potential peaks differ as a function of peak latency. In general, early latency peaks reflect the transmission of afferent sensory information, and changes in either the latency or amplitude of these peaks generally indicate a neurotoxic change that is likely to be reflected in deficits in sensory perception. The later latency peaks, in general, reflect not only the sensory input, but also the more nonspecific factors such as the behavioral state of the subject including such factors as arousal level, habituation, or sensitization. Thus, the neurotoxicological significance of changes in later latency evoked potential peaks must be interpreted in light of the behavioral status of the subject.

4.3.3.3. Convulsions.

Observable behavioral convulsions in animals may be indicative of central nervous system seizure activity. However, behavioral convulsions that occur only at lethal or near lethal dose levels may reflect an indirect effect secondary to systemic toxicity and not directly on the nervous system. Convulsions occurring at dose levels that are clearly sublethal, and in the absence of apparent systemic toxicity, are more likely due to a direct effect on the nervous system. In such cases, neurophysiological recordings of electrical activity in the brain that are indicative of seizures may provide

additional evidence of direct neurotoxicity. In addition to producing seizures, chemicals may also affect seizure susceptibility, altering the frequency, severity, duration, or threshold for eliciting seizures produced through other means. Such changes can occur after acute exposure or after repeated exposure to dose levels below the acute threshold, and are considered neurotoxic. Agents that produce convulsions include lindane, DDT, pyrethroids, and trimethyltin (WHO, 1986). Some agents, including many solvents, act to raise the threshold for eliciting seizures through other means or otherwise act to reduce the severity or duration of the elicited convulsions. These agents are difficult to classify as neurotoxic based on such data, but frequently have other effects on which a determination of neurotoxic potential can be based.

4.3.3.4. Electroencephalography (EEG)

EEG analysis is used widely in clinical settings for the diagnosis of neurological disorders and less often for the detection of subtle toxicant-induced dysfunction (WHO, 1986; Eccles, 1988). The basis for the use of EEG in either setting is the relationship between specific patterns of EEG waveforms and specific behavioral states. Because states of alertness and the stages of sleep are associated with distinct patterns of electrical activity in the brain, it is generally thought that arousal level can be evaluated by monitoring the EEG. Dissociation of EEG activity and behavior can, however, occur after exposure to certain chemicals. Normal patterns of transition between sleep stages or between sleeping and waking states are known to remain disturbed for prolonged periods of time following exposure to certain chemical classes (e.g., organophosphates). Changes in the pattern of the EEG can be elicited by stimuli producing arousal (e.g., lights, sounds) and neuroactive drugs. In studies with toxicants, changes in EEG pattern can sometimes precede alterations in other objective signs of neurotoxicity. EEG experiments must be done under highly controlled conditions, and the neurotoxicological significance of chemical-induced changes in the EEG in the absence of other signs of neurotoxicity must be considered on a case-by-case basis. Many chemicals, including metals, solvents, and pesticides, would be expected to affect the EEG.

4.3.3.5. Electromyography (EMG).

EMG involves making electrical recordings from muscle and has been used extensively in human clinical

studies in the diagnosis of certain diseases of the muscle (WHO, 1986). Changes in the EMG include amplitude and firing frequency of spontaneous firing; evoked muscle responses to nerve stimulation can be used to study alterations in the neuromuscular junction. EMG has been used to study toxicant-induced changes in neuromuscular function, including organophosphate insecticides, methyl n-butyl ketone, and botulinum and tetanus toxin.

4.3.3.6. Spinal reflex excitability.

Segmental spinal monosynaptic and polysynaptic reflexes are relatively simple functions in the central nervous system that can be evaluated by quantitative techniques (WHO, 1986). Many of the procedures used in animals are similar to procedures used clinically to perform neurological tests in humans. One approach infers the functional state of a reflex arc from either the latency and magnitude of the reflex response evoked by stimuli of predetermined intensity or from the stimulus intensity required to elicit a detectable response (i.e., the threshold). This approach is used best in a screening context and the significance of effects in this test should be considered on a case-by-case basis.

A second more involved approach records electrophysiologically the time required for a stimulus applied to a peripheral nerve to reach the spinal cord and return to the site of the original stimulation. Data from this procedure can indicate the excitability of the motoneuron pool, an effect seen with many volatile solvents. Although this approach is more invasive and time-consuming than the noninvasive procedure, it provides better data concerning the possible site of action. In addition, the manner in which the invasive procedure is carried out (i.e., in decerebrated animals) precludes repeated testing on the same animal. The significance of effects in this procedure should also be considered on a case-by-case basis.

4.3.4. Neurochemical Endpoints of Neurotoxicity

Neuronal function within the nervous system is dependent on synthesis and release of specific neurotransmitters and activation of their receptors in specific neuronal pathways. With few exceptions, neurochemical measurements are invasive and therefore used infrequently in human risk assessment. There are many different neurochemical endpoints that could be measured in neurotoxicological studies (Bondy, 1986; Mailman, 1987; Morell and

Mailman, 1987). Neurotoxicants can interfere with the ionic balance of a neuron, act as a cytotoxicant after being transported into a nerve terminal, block uptake of neurotransmitter precursors, act as a metabolic poison, overstimulate

receptors, block transmitter release, and inhibit transmitter degradation. Table 4-4 lists several chemicals with known neurochemical effects. Many neuroactive agents can increase or decrease neurotransmitter levels in the

brain. Dose-related changes on these endpoints may indicate a chemical effect on the nervous system, but the neurotoxicological significance of such changes must be interpreted in the context of other signs of neurotoxicity.

TABLE 4-4.—NEUROTOXICANTS WITH KNOWN NEUROCHEMICAL MECHANISMS

Site of attack	Examples
1. Neurotoxicants acting on ionic balance	
A. Inhibit sodium entry	Tetrodotoxin.
B. Block closing of sodium channel	p,p'-DDT, pyrethroids (I).
C. Increase permeability to sodium	Batrachotoxin.
D. Increase intracellular calcium	Chlordecone.
2. Cytotoxicants—depend on uptake into nerve terminal	MPTP.
3. Uptake blockers	Hemicholinium.
4. Metabolic poisons	Cyanide.
5. Receptor hyperactivators	Domoic acid.
6. Transmitter release (ACh) blockers	Botulinum toxin.
7. Transmitter degradation (ACh) inhibitors	Organophosphates, carbamates.
8. Microtubule disruptors	Vincristine.

Some chemicals, such as the organophosphate and carbamate insecticides, are known to interfere with a specific enzyme, acetylcholinesterase (AChE) (Costa, 1988). Inhibition of this enzyme in brain may be considered evidence of neurotoxicity, whereas decreases in AChE in the blood, which can be easily determined in humans, are only suggestive of a neurotoxic effect. A subset of organophosphate agents produces organophosphate-induced delayed neuropathy (OPIDN) after acute or repeated exposure. Neurotoxic esterase (or neuropathy target enzyme, NTE) has been associated with agents that produce OPIDN (Johnson, 1990).

The ultimate functional significance of many biochemical changes is not known; therefore it may be difficult to determine if a specific biochemical

change can be considered adverse or convincing evidence of neurotoxicity. Any such change, however, is potentially adverse and each determination of adversity requires a judgment to be made. Likewise, the absence of specific biochemical testing protocols does not mean biochemical changes are of no concern, but instead reflects a lack of understanding of the significance of changes at the biochemical level.

4.3.5. Structural Endpoints of Neurotoxicity

The central nervous system (brain and spinal cord) comprises nerve cells or neurons, which consist of a neuronal body, axon, and dendritic processes. Various types of neuropathological lesions may be classified according to

their nature or the site where they are found (WHO, 1986; Krinke, 1989; Griffin, 1990). Lesions may be classified as neuropathy (changes in the neuronal body), axonopathy (changes in the axons), myelinopathy (changes in the myelin sheaths), neurodegeneration (changes in the nerve terminals), and peripheral neuropathy (changes in the peripheral nerves). For axonopathies, a more precise location of the changes should be described (i.e., proximal, central, or distal axonopathy). In some cases, agents produce neuropathic conditions that resemble naturally occurring neurodegenerative disorders in humans (WHO, 1986). Table 4-5 lists examples of such chemicals, their known site of action, the type of neuropathology produced, and the disease or condition that each typifies.

TABLE 4-5.—EXAMPLES OF KNOWN NEUROPATHIC AGENTS

Site of attack	Neuropathology	Corresponding neurotoxicant	Disease or neurodegenerative condition
Neuron cell body	Neuronopathy	Methylmercury .. A.E.T.T. Quinolinic acid .. 3-acetylpyridine .. Aluminum	Minamata disease. Ceroid lipofuscinoses. Huntington's disease. Cerebellar ataxia. Alzheimer's disease.
Nerve terminal	Neurodegeneration	MPTP	Parkinson's disease.
Schwann cell myelin	Myelinopathy	Lead Buckthorn toxin. Acrylamide .. Hexacarbons .. Carbon disulfide ..	Neuropathy of metachromatic leukodystrophy. Vitamin deficiency.
Central-peripheral distal axon	Distal axonopathy	Clioquinol	Subacute myelo-optico-neuropathy.
Central axons	Central axonopathy	B,B'-iminodipropionitrile.	Motor neuron disease.
Proximal axon	Proximal axonopathy		

In general, chemical effects lead to two types of primary cellular alteration: (1) the accumulation, proliferation, or rearrangement of structural elements (e.g., intermediate filaments, microtubules) or organelles (mitochondria) and (2) the breakdown of cells, in whole or in part. The latter can be associated with regenerative processes that may occur during chemical exposure. Such changes are considered to be neurotoxic.

While most neurotoxic damage is evident at the microscopic level, gross changes in morphology can be reflected by a significant change in the weight of the brain. Weight changes (absolute or relative to body weight), discoloration, discrete or massive cerebral hemorrhage, or obvious lesions in nerve tissue are generally considered neurotoxic effects.

Chemical-induced injury to the central nervous system is associated with astrocytic hypertrophy at the site of damage. Assays of glial fibrillary acidic protein (GFAP), the major intermediate filament protein of astrocytes, has been proposed as a biomarker of this response (O'Callaghan, 1988). A number of chemicals known to injure the central nervous system, including trimethyltin, methylmercury, cadmium, 3-acetylpyridine, and MPTP, have been shown to increase GFAP. In addition, increases in GFAP may be seen at dosages below those necessary to produce cytopathology as determined by Nissl-based stains used in standard neuropathological examinations. Because increases in GFAP may be an early indicator of neuronal injury in the adult, exposure level-dependent increases in GFAP should be viewed with concern.

Chemical-induced alterations in the structure of the nervous system are generally considered neurotoxic effects. To ensure reliable data, it is important that neuropathological studies minimize fixation artifacts and potential differences in the section(s) of the nervous system sampled and control for variability due to the age, sex, and body weight of the subject (WHO, 1986).

4.3.6. Developmental Neurotoxicity

Exposure to chemicals during development can result in effects other than death, gross structural abnormality, or altered growth. There are several instances in which functional alterations have resulted from exposure during the period between conception and sexual maturity (Riley and Vorhees, 1986; Vorhees, 1987). Table 4-6 lists several examples of chemicals known to produce developmental neurotoxicity in experimental animals. Animal models

of developmental neurotoxicity have been shown to be sensitive to several environmental chemicals known to produce developmental toxicity in humans, including lead, ethanol, methylmercury, and PCBs (Kimmel et al., 1990).

TABLE 4-6.—PARTIAL LIST OF AGENTS BELIEVED TO HAVE DEVELOPMENTAL NEUROTOXICITY

Alcohols	Methanol, ethanol
Antimitotics	X-radiation, azacytidine
Insecticides	DDT, kepone, organophosphates
Metals	Lead, methylmercury, cadmium
Polyhalogenated hydrocarbons	PCB, PBB
Psychoactive drugs	Cocaine, phenytoin
Solvents	Carbon disulfide, toluene
Vitamins	Vitamin A

Sometimes functional defects are observed at dose levels below those at which other indicators of developmental toxicity are evident (Rodier, 1986). Such effects may be transient or reversible in nature, but generally are considered adverse effects. Data from postnatal studies, when available, are considered useful for further assessment of the relative importance and severity of findings in the fetus and neonate. Often, the long-term consequences of adverse developmental outcomes noted at birth are unknown and further data on postnatal development and function are necessary to determine the full spectrum of potential developmental effects. Useful data also can be derived from well-conducted multigeneration studies, although the dose levels used in these studies may be much lower than those in studies with shorter-term exposure.

Much of the early work in developmental neurotoxicology was related to behavioral evaluations. Recent advances in this area have been reviewed in several publications (Riley and Vorhees, 1986; Kimmel et al., 1990). Several expert groups have focused on the functions that should be included in a behavioral testing battery, including sensory systems, neuromotor development, locomotor activity, learning and memory, reactivity and habituation, and reproductive behavior. No testing battery has fully addressed all of these functions, but it is important to include as many as possible, and several testing batteries have been developed and evaluated for use in testing.

Direct extrapolation of functional developmental effects to humans is limited in the same way as for other endpoints of developmental toxicity, i.e., by the lack of knowledge about underlying toxicological mechanisms and their significance. It can be assumed that functional effects in animal studies indicate the potential for altered development in humans, although the types of developmental effects seen in experimental animal studies will not necessarily be the same as those that may be produced in humans. Thus, when data from functional developmental toxicity studies are encountered for particular agents, they should be considered in the risk assessment process.

Agents that produce developmental neurotoxicity at a dose that is not toxic to the maternal animal are of special concern because the developing organism is affected but toxicity is not apparent in the adult. More commonly, however, adverse developmental effects are produced only at doses that cause minimal maternal toxicity; in these cases, the developmental effects are still considered to represent developmental toxicity and should not be discounted as secondary to maternal toxicity. At doses causing excessive maternal toxicity (that is, significantly greater than the minimal toxic dose), information on developmental effects may be difficult to interpret and of limited value. Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; it may be that the mother and developing organism are sensitive to that dose level. Moreover, whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while effects on the offspring may be permanent. These are important considerations for agents to which humans may be exposed at minimally toxic levels either voluntarily or involuntarily, because several agents are known to produce adverse developmental effects at minimally toxic doses in adult humans (e.g., smoking, alcohol).

Although interpretation of functional developmental neurotoxicity data may be limited at present, it is clear that functional effects must be evaluated in light of other toxicity data, including other forms of developmental toxicity (e.g., structural abnormalities, perinatal death, and growth retardation). The level of confidence in an adverse effect may be as important as the type of change seen, and confidence may be increased by such factors as replicability of the effect either in another study of

the same function or by convergence of data from tests that purport to measure similar functions. A dose-response relationship is considered an important measure of chemical effect; in the case of functional effects, both monotonic and biphasic dose-response curves are likely, depending on the function being tested.

4.3.7. Physiological and Neuroendocrine Endpoints

One of the key roles played by the nervous system is to orchestrate the general physiological functions of the body to help maintain homeostasis. To this end, the nervous system and many of the peripheral organ systems are integrated and functionally interdependent. For example, specific neuronal processes are intimately involved in maintaining or modulating respiration, cardiovascular function, body temperature, and gastrointestinal function. Because many peripheral organ functions involve neuronal components, changes in such physiological endpoints as blood pressure, heart rate, EKG, body temperature, respiration, lacrimation, or salivation may indirectly reflect possible treatment-related effects on the functional integrity of the nervous system. However, since physiological endpoints also depend on the integrity of the related peripheral organ itself, changes in physiological function also may reflect a systemic toxicity involving that organ. Consequently, the neurotoxicological significance of a physiological change must be interpreted within the context of other signs of toxicity. A variety of general physiological procedures can be applied to neurotoxicological problems. These procedures range in scale from simple measurements, for example, of body temperature, respiration, lacrimation, salivation, urination, and defecation, which may be included in routine functional observational batteries used for chemical screening, to more involved procedures involving measurements of blood pressure, endocrine responses, cardiac function, gastrointestinal function, etc. The latter would be more appropriate for second-level tests to characterize the scope of chemically related toxicity.

The central nervous system also regulates the outflow of the endocrine system, which together with the influence of the autonomic nervous system, can affect immunologic function (WHO, 1986). Hormonal balance results from the integrated action of the hypothalamus, located in the central nervous system, and the pituitary, which regulates activities of endocrine

target organs. Each site is susceptible to disruption by neurotoxic agents. Neuroendocrine dysfunction may occur because of a disturbance in the regulation and modulation of the neuroendocrine feedback systems. One major indicator of neuroendocrine function is secretions of hormones from the pituitary. Hormones from the anterior pituitary are important for reproduction (follicle-stimulating hormone, luteinizing hormone), growth (thyroid-stimulating hormone), and response to stress (adrenocorticotrophic hormone). Hypothalamic control of anterior pituitary secretions occurs through the release of hypothalamic-hypophyseotropic hormones. Hormones from the posterior hypothalamus (prolactin, melanocyte-stimulating hormone, and growth hormone) are also involved in a number of important bodily functions.

Many types of behaviors (e.g., reproductive behaviors, sexually dimorphic behaviors) are dependent on the integrity of the hypothalamic-pituitary system, which could represent an important site for neurotoxic action. Pituitary secretions arise from a number of different cell types in this gland and neurotoxicants could affect these cells either directly or indirectly. Morphological changes in follicular cells, chromophobe cells, somatotrophic cells, prolactin cells, gonadotrophic cells, follicle-stimulating hormone secreting cells, luteinizing hormone-containing cells, thyrotrophic cells, and cortico cells might be associated with adverse effects on the pituitary, which could ultimately affect behavior and the functioning of the nervous system.

Biochemical changes in the hypothalamus also may be used as indices of potential changes in neuroendocrine function. However, the neuroendocrine significance of changes in hypothalamic neurotransmitters and neuropeptides is usually only inferential and data must be considered on a case-by-case basis.

Most anterior pituitary hormones are subject to negative feedback control by peripheral endocrine glands and, if neurotoxicants modify peripheral secretions, neuroendocrine changes can result from this altered feedback. Modifications in the functioning of these endocrine secretions could occur after toxic exposure; a number of agents have been shown to alter blood levels of glucocorticoids, thyroxine, estrogen, corticosterone, and testosterone. Although such changes are not necessarily due to direct neuroendocrine effects, target organ changes often can be a first indication of neuroendocrine changes.

4.3.8. Other Considerations

4.3.8.1. Structure-activity relationship.

Because of a general lack of epidemiologic or toxicologic data on most chemical substances, attempts have been made in toxicology to predict activities based on chemical structure. The basis for inference from structure-activity relationships (SARs) can be either comparison with structures known to have biologic activity or knowledge of structural requirements of a receptor or macromolecular site of action. However, given the complexity of the nervous system and the lack of information on biologic mechanisms of neurotoxic action, there are relatively few well-characterized SARs in neurotoxicology. Since SARs cannot be used to rule out all neurotoxic activity, it is not acceptable to use them as a basis for excluding potential neurotoxicity. Caution is warranted in interpreting SARs in anything other than the most preliminary analyses. Use of SARs requires detailed knowledge not only of structure, but also of each critical step in the pathogenetic mechanism of neurotoxic injury. Such knowledge is still generally unavailable.

SAR approaches are more successful when the range of possible sites of action or mechanisms of action is narrow. Thus, SARs have had more use in relation to carcinogenicity and mutagenicity than in other kinds of toxicity. The SAR approaches used in the development of novel neuropharmacologic structures deserve consideration in neurotoxicology, but their utility depends on a better understanding of neurotoxic mechanisms.

4.3.8.2. In vitro methods.

In vitro procedures for testing have practical advantages, but studies must be done to correlate the results with responses in whole animals. One advantage of validated in vitro tests is that they minimize the use of live animals. Some of the more developed in vitro tests might be simple and might not have to be conducted by highly trained personnel, but, as with many in vivo tests, the analysis and interpretation of results are likely to require expertise. Experience with the Ames test for mutagenesis confirms the advantages of in vitro procedures, but also illustrates the problems that arise when an assay is used to predict an endpoint that is not exactly what it measures (e.g., carcinogenicity rather than specific aspects of genotoxicity). In vitro changes can be markers for toxicity, even when the structural or functional consequences are not known

or predicted. In addition, *in vitro* methods can examine the more evolutionarily conserved elements of the nervous system and improve neurotoxicity detection and could also provide suitable systems for studying developmental neurotoxicity.

A broad range of tissue-culture systems are available for assessing the neurologic impact of environmental agents, including cell lines, dissociated cell cultures, reaggregate cultures, explant cultures, and organ cultures (Veronesi, 1991).

Neuronal and glial cell lines are used extensively in neurobiology and have potential for neurotoxicological studies. They consist of populations of continuously dividing cells that, when treated appropriately, stop dividing and exhibit differentiated neuronal or glial properties. Neuronal lines can develop electric excitability, chemosensitivity, axon formation, neurotransmitter synthesis and secretion, and synapse formation. Large quantities of cells can be generated routinely to develop extensive dose-response or other quantitative data.

When neural tissue, typically from fetal animals, is dissociated into a suspension of single cells, and the suspension is inoculated into tissue-culture dishes, the neurons and glia survive, grow, and establish functional neuronal networks. Such preparations have been made from most regions of the CNS and exhibit highly differentiated, site-specific properties that constitute an *in vitro* model of different portions of the CNS. Most of the neuronal transmitter and receptor phenotypes can be demonstrated, and a variety of synaptic interactions can be studied. Glial cells are also present, and neuroglial interactions are a prominent feature of the cultures. A substantial battery of assays (neurochemical and neurophysiologic) is now available to assess the development of the cultures and to indicate toxic effects of test agents added to the culture medium. Relatively pure populations of different cell types can be isolated and cultured, so that effects on specific cell types can be assessed independently. Pure glial cells or neurons, or even specific neural categories, can be prepared in this way and studied separately, or interaction between neurons and glial cells can be studied at high resolution. The neurobiologic measures used to assess the effect of any agent can be very specific (for example, activity of neurotransmitter-related enzyme or binding of a receptor ligand) or global (for example, neuron survival or concentration of glial fibrillary acidic protein). The two-dimensional character

of the preparations makes them particularly suited for morphologic evaluation, and detailed electrophysiologic studies are readily performed. The toxic effects and mechanisms of anticonvulsants, excitatory amino acids, and various metals and divalent cations have been assessed with these preparations. The cerebellar granular cell culture system, for example, has been exploited recently in studies of the mechanism of alkyllead toxicity (Verity et al., 1990).

A related preparation made from single-cell suspensions of neural tissue is the reaggregate culture. Instead of being placed in culture dishes and allowed to settle onto the surface of the dishes, the cells are kept in suspension by agitation; under appropriate conditions, they stick to one another and form aggregates of controllable size and composition. Typically, the cells in an aggregate organize and exhibit intercellular relations that are a function of, and bear some resemblance to, the brain region that was the source of the cells. The cells establish a three-dimensional, often laminated structure. Reaggregate cultures lend themselves to large-scale, quantitative experiments in which neurobiologic variables can be examined, although morphologic and ligand-binding studies are performed less readily than with surface cultures.

Organotypic explant cultures also are closely related to the intact nervous system. Small pieces or slices of neural tissue are placed in culture and can be maintained for long periods with substantial maintenance of structural and cell-cell relations of intact tissue. Specific synaptic relations develop and can be maintained and evaluated, both morphologically and electrophysiologically. Because all regions of the nervous system are amenable to this sort of preparation, it is possible to analyze toxic agents that are active only in specific regions of the central or peripheral nervous system. Explants can be made from relatively thin slices of neural tissue, so detailed morphologic and intracellular electrophysiologic studies are possible. Their anatomic integrity is such that they capture many of the cell-cell interactions characteristic of the intact nervous system while allowing a direct, continuing evaluation of the effects of a potentially neurotoxic compound added to the culture medium. The process of myelination has been studied extensively in explant cultures, and considerable neurotoxicologic information has been gained. A preparation similar to an explant culture is the organ culture, in which an entire organ, such as the inner ear or a

ganglion, rather than slices or fragments, is grown *in vitro*. Obviously, only structures so small that their viability is not compromised can be treated in this way.

In general, the technical ease of maintaining a culture varies inversely with the degree to which it captures a spectrum of *in vivo* characteristics of nervous system behavior. The problem of biotransformation of potentially neurotoxic compounds is shared by all, although the more complete systems (explant or organ cultures) might alleviate this problem in specific instances. In many culture systems, complex and ill-defined additives—such as fetal calf serum, horse serum, and human placental serum—are used to promote cell survival. A number of thoroughly described synthetic media are now available, however, and such fully defined culture systems can be used where necessary.

5. Neurotoxicology Risk Assessment

5.1. Introduction

Risk assessment is an empirically based process used to estimate the risk that exposure of an individual or population to a chemical, physical, or biological agent will be associated with an adverse effect. Generally, such effects can be quantified and the relative probability of their occurrence can be calculated. The risk assessment process usually involves four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization (NRC, 1983). Risk management is the process that applies information obtained through the risk assessment process to determine whether the assessed risk should be reduced and, if so, to what extent (NRC, 1983). In some cases, risk is the only factor considered in a decision to regulate exposure to a substance. Alternatively, the risk posed by a substance is weighed against social, ethical, and medical benefits and economic and technological factors in formulating a risk management decision. The risk-balancing approach is used by some agencies to consider the benefits as well as the risks associated with unrestricted or partially restricted use of a substance. The purpose of this chapter is to describe the risk assessment process as it has currently evolved in neurotoxicology and present available options for quantitative risk assessment.

5.2. The Risk Assessment Process

5.2.1. Hazard Identification

Agents that adversely affect the neurophysiological, neurochemical, or

structural integrity of the nervous system or the integration of nervous system function expressed as modified behavior may be classified as neurotoxicants (Tilson, 1990b). For hazard identification, the best or most generalizable studies would measure these changes in humans. With the exclusion of therapeutic agents, information on effects in humans is usually derived from case reports of accidental exposures and epidemiological studies. This type of data affords less certainty regarding generalizability as well as less specific exposure information. As discussed in chapter 4, a common alternative method of data generation for hazard identification is the use of animal models. Animal models that measure behavioral, neurophysiological, neurochemical, and structural effects have been developed and validated. Studies that employ these models to evaluate specific potential hazards are used to predict the outcome of exposure to the same hazard in humans.

5.2.1.1. Human studies

Information obtained through the evaluation of human exposure data provides direct identification of neurotoxic hazards. This type of information is generally available from clinical trials required for the approval of therapeutic products for human use. For the purposes of risk assessment of nontherapeutic substances, data on effects of exposure to humans come primarily from two types of studies: case reports and epidemiological (Friedlander and Hearn, 1980) (see chapter 3). Case studies can supply evidence of an agent's toxicity, but are often limited by both the qualitative nature of the signs and symptoms reported and the nature of the exposure data. Epidemiological studies can provide data on the types of neurotoxic effects and the possible susceptibilities of certain populations. Under appropriate considerations, they can generally provide convincing and reliable evidence of potential human neurotoxicity. As with case studies, however, often only qualitative estimates of exposure can be obtained. Controlled laboratory studies have the potential to provide adequate exposure and effects data for accurate hazard identification, but ethical considerations place moral and practical restrictions on such studies except in those instances where direct benefit to the subjects, as in the case of therapeutic agents, may be expected. Excluding instances of therapeutic product development, most studies are limited to measuring the effects of acute, rather than long-term,

exposure. This limits their utility in risk assessment because the effect of long-term, low-level exposure to a potentially toxic agent is often the issue of concern.

Methods available to evaluate neurotoxicity in humans include examination of neurophysiological and behavioral parameters. Specific tests to measure neuromuscular strength and coordination, alterations in sensation, deficits in learning and memory, changes in mood and personality, and disruptions of autonomic function are frequently employed (see chapter 3).

5.2.1.2. Animal studies

As discussed in chapter 4, animal models for many endpoints of neurotoxicity are available and widely used for hazard identification. Data from animal studies are frequently extrapolated to humans. For example, if exposure to an agent produces neuropathology in an animal model, damage to a comparable structure in humans is predicted. Similarly, biochemical and physiological effects observed in animals are commonly extrapolated to humans. Agents that produce alterations in the levels of specific enzymes in one animal species generally have the same effect in other species, including humans. Neurophysiological endpoints also tend to be affected by the same manipulations across species. Thus, an agent interfering with nerve conduction in an animal study is often assumed to have the same effect in humans. Behavioral studies in animals are also applied to human hazard identification, although the correspondence between methods employed in animals and humans is sometimes not as obvious. For this reason, behavioral methods developed for neurotoxic hazard identification need to be considered on a case-by-case basis.

5.2.1.3. Special issues

5.2.1.3.1. Animal-to-human extrapolation. The use of animal data to identify hazard to humans is not without controversy. Relative sensitivity across species as well as between sexes is a constant concern. Overly conservative risk assessments, based on the assumption that humans are always more sensitive than a tested animal species, can result in poor risk management decisions. Conversely, an assumption of equivalent sensitivity in a case where humans actually are more sensitive to a given agent can result in underregulation that might have a negative impact on human health.

5.2.1.3.2. Susceptible populations. A related controversy concerns the use of data collected from adult organisms,

animal or human, to predict hazards in potentially more sensitive populations, such as the very young and the elderly, or in other groups, such as the chronically ill. In some cases, identification of neurotoxicity hazard does not generally include subjects from either end of the human life span or from other than healthy subjects. Uncertainty factors are used to adjust for more sensitive populations. In addition, single or multigeneration reproductive studies in animals may provide a source of information on neurological disorders, behavioral changes, autonomic dysfunction, neuroanatomical anomalies, and other signs of neurotoxicity in the developing animal (chapter 4).

5.2.1.3.3. Reversibility. For the most part, the basic principles of hazard identification are the same for neurotoxicity as for any adverse effect on health. One notable exception, however, concerns the issue of reversibility and the special consideration that must be given to the inherent redundancy and plasticity of the nervous system.

For many health effects, temporary, as opposed to permanent, effects are repaired during a true recovery. Damage to many organ systems, if not severe, can be spontaneously repaired. For example, damaged liver cells that may result in impaired liver function often can be replaced with new cells that function normally. The resulting restoration of liver function can be viewed as recovery. In the central nervous system, cells generally do not recover from severe damage and new cells do not replace them. When nervous system recovery is observed, it may represent compensation requiring activation of cells that were previously performing some other function, reactive synaptogenesis, or recovery of moderately injured cells. While a damaged liver may recover due to the addition of new cells, severe damage to nervous system cells results in a net loss of cells. This loss of compensatory capacity may not be noticed for many years and, when it does appear, it may be manifest in a way seemingly unrelated to the original neurotoxic event. Lack of ability to recover from a neurotoxic event later in life or premature onset of signs of normal aging may result. It is therefore important to consider the possibility that significant damage to the nervous system may have occurred in experiments where effects appear to be reversible.

5.2.1.3.4. Weight of evidence.

A "weight of evidence" approach to identifying an agent as a neurotoxic

hazard is almost always necessary. With the exception of therapeutic products, a single, complete, controlled study of an agent's effects on the nervous system, conducted in an appropriate representative sample of humans, is rarely, if ever, possible. Rather, those individuals charged with identifying hazard are usually confronted with a collection of imperfect studies, often providing conflicting data (Barnes and Dourson, 1988).

There are several possible approaches, depending on the quality of the evidence. Two examples are the use of data from only the most sensitive species tested and the use of data from only species responding most like the human for any given endpoint. In assessing neurotoxicity of therapeutic products, when human data are available and neurotoxic endpoints detected in animals can be clinically measured, the human findings supersede those of the nonclinical data base. Assuming that all available evidence is to be included, considerations necessary for formulating a conclusion include the relative weights that should be given to positive and negative studies. Sometimes positive studies are given more weight than negative ones, even when the quality of the studies is comparable. Experimental design factors such as the species tested, the number and gender of subjects evaluated, and the duration of the test are given different weights when data from different studies are combined. The route of exposure in a given study and its relevance to expected routes of human exposure are often a weighted factor. The issue of statistical significance is frequently debated. Some argue that an effect occurring at a statistically insignificant level may nevertheless represent a biologically or toxicologically significant event, and should be afforded the same weight as if the finding were statistically significant. In general, however, only statistically significant measures should be considered in hazard identification. The power of various statistical measures is also considered.

5.2.2. Dose-Response Assessment

In the second step of the risk assessment process, the dose-response assessment, the relationship between the extent of damage or toxicity and dose of a toxic substance for various conditions of exposure is determined. Because several different kinds of responses may be elicited by a single agent, more than one dose-response relationship may need to be developed

(e.g., neurochemical and morphological parameters).

When quantitative human dose-effect data are not available for a sufficient range of exposures, other methods must be used to estimate exposure levels likely to produce adverse effects in humans. In the absence of human data, the dose-response assessment may be based on tests performed in laboratory animals. Evidence for a dose-response relationship is an important criterion in assessing neurotoxicity, although this may be based on limited data from standard studies that often use only three dose groups and a control group (Barnes and Dourson, 1988).

The most frequently used approach for risk assessment of neurotoxicants and other noncancer endpoints is the uncertainty- or safety-factor approach (Barnes and Dourson, 1988; Kimmel, 1990). For example, within the EPA, this approach involves the determination of reference doses (RfDs) by dividing a no observed adverse effect level (NOAEL) by uncertainty factors that presumably account for interspecies differences in sensitivity (Barnes and Dourson, 1988). Generally, an uncertainty factor of 10 is used to allow for the potentially higher sensitivity in humans than in animals and another uncertainty factor of 10 is used to allow for variability in sensitivity among humans. Hence, the RfD is equal to the NOAEL divided by 100. If the NOAEL cannot be established, it is replaced by the lowest observed adverse effect level (LOAEL) in the RfD calculation and an additional uncertainty factor of 10 is introduced (i.e., the RfD equals the LOAEL divided by 1000).

If more than one effect is observed in the animal bioassays, the effect occurring at the lowest dose in the most sensitive animal species and gender is generally used as the basis for estimating the RfD (OTA, 1990). Sometimes, different RfDs can be calculated, depending on endpoint or species selected. Selection of safety factors may be influenced by several considerations, including data available from humans, weight of evidence, type of toxic insult, and probability of variations in responses among susceptible populations (e.g., very young or very old). Established guidelines have been accepted by several agencies that use the safety-factor approach to account for intraspecies variability, cross-species extrapolation, and exposure duration. In some instances, comparisons between these predicted values and experimental data have been conducted and the results appear comparable for some

selected examples (Dourson and Stara, 1983; McMillan, 1987).

The uncertainty-factor approach is based on the assumption that a threshold does exist, that there is a dose below which an effect does not change in incidence or severity. The threshold concept is complicated and controversial. As described by Sette and MacPhail (1992), there are several different ways in which the term threshold is used. Thresholds are defined, in part, by the limit of detection of an assay. As the sensitivity of the analytical method or bioassay is improved, the threshold might be adjusted downward, indicating that the true threshold had not been previously determined.

Another problem inherent with an observation of no discernible effects at low doses is that it is impossible to determine whether the risk is actually zero (i.e., the dose is below a threshold dose) or whether the statistical resolving power of a study is inadequate to detect small risks (Gaylor and Slikker, 1992). Every study has a statistical limit of detection that depends on the number of individuals or animals involved. For example, it would be relatively unusual to conduct an experiment on a neurotoxicant with as many as 100 animals per dose. If no deleterious effects were observed in 100 animals at a particular dose, it might be concluded that this dose level is below the threshold dose. However, we can only be 95 percent confident that the true risk is less than 0.03. That is, if 3 percent of the animals in a population actually develop a toxic effect at this dose, there is a 5 percent chance that a group of 100 animals would not show any effect. The observation of no toxic effects in an extremely large sample of 1,000 animals only indicates with 95 percent confidence that the true risk is less than 0.003, etc. Because thresholds cannot be realistically demonstrated, they are therefore assumed.

The notion of threshold may be useful in explaining mechanisms associated with specific types of toxicity. What little is known about mechanisms of neurotoxicity suggests that both threshold and nonthreshold scenarios are possible (Silbergeld, 1990). However, for one of the most studied neurotoxicants, lead, there has been a steady decline in exposure levels shown to have effects, suggesting to some that no threshold dose is apparent (Bondy, 1985). Sette and MacPhail (1992) also consider the threshold as a mathematical assumption and as a population sensitivity and conclude that "the idea of no threshold seems experimentally untestable. . . ."

The RfD approach relies on single experimental observations (the NOAEL or LOAEL) instead of complete dose-response curve data to calculate risk estimations. Chemical interactions with biological systems are often specific, stereoselective, and saturable. Examples include enzyme-substrate binding leading to substrate metabolism, transport, and receptor-binding, any or all of which may be a requirement of an agent's effect or toxicity. Therefore, a chemical's dose-response curve may not be linear. The certainty of low-dose extrapolation has been determined to be markedly affected by the shape of the dose-response curve (Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation, 1971). Therefore, the appropriate use of dose-response curve data should enhance the certainty of risk estimations when thresholds are not assumed or determined.

Dose-response models have generated considerable interest as more appropriate and quantitative alternatives to the safety-factor approach in risk assessment. Rather than routinely applying a "fixed" safety factor to the NOAEL (based on a single dose) to obtain a "safe" dose, another approach uses data from the entire dose-response curve.

Two fundamentally different approaches in the use of dose-response data to estimate risk have been developed. Dews and coworkers (Dews, 1986; Glowa and Dews, 1987; Glowa et al., 1983) and Crump (1984) demonstrated an approach in which they used information on the shape of the dose-response curve to estimate levels of exposure associated with relatively small effects (i.e., a 1, 5, or 10 percent change in a biological endpoint). Both Dews and Crump fit a mathematical function to the data and provided an estimate of the variability in exposure levels associated with a relatively small effect.

An alternative approach developed by Gaylor and Slikker (1990) first establishes a mathematical relationship between a biological effect and the dose of a given chemical. The second step determines the distribution (variability) of individual measurements of biological effects about the dose-response curve. The third step statistically defines an adverse or "abnormal" level of a biological effect in an untreated population. The fourth step estimates the probability of an adverse or abnormal level as a function of dose utilizing the information from the first three steps. The advantages of these dose-response models are that they encourage the generation and use

of data needed to define a complete dose-response curve.

Although more quantitative dose-response assessment models have emerged in recent years, uncertainty remains as to what biological endpoints from which species with what dosing regimen should be analyzed. Within a species, a given agent may produce a variety of effects, including neurochemical, neuropathological, and behavioral effects. In other instances, a chemical may produce alterations of one endpoint but not others (Slikker et al., 1989). Species selection may also dramatically affect the outcome of risk assessments. The Parkinson-like syndrome produced by single doses of MPTP in the human or nonhuman primate is not observed in rats given comparable MPTP doses (Kopin and Markey, 1988). Although endpoint and species selection appear to have a tremendous effect on the outcome of an assessment, only a few studies have systematically investigated the effect on assessment outcome of varying either the species or the endpoint within a species (McMillan, 1987; Hattis and Shapiro, 1990; Gaylor and Slikker, 1992).

5.2.3. Exposure Assessment

This step of the risk assessment process determines the source, route, dose, and duration of human exposure to an agent. The results of the dose-response assessment are combined with an estimate of human exposure to obtain a quantitative estimate of risk. As either the effect of or the exposure to an agent approaches zero, the risk of neurotoxicity approaches zero. It should be recognized that exposures to multiple agents may produce synergistic or additive effects.

Exposure can occur via many routes, including ingestion, inhalation, or contact with skin. Sources of exposure may include soil, food, air, water, or intended vehicle (e.g., drug formulation). The degree of exposure may be strongly influenced by a number of factors, for example, the occupation of the individual involved.

The duration of exposure (i.e., acute or chronic) and interval of exposure (i.e., episodic or continuous) are variables of exposure that are common to all types of risk assessments, including carcinogenicity (OSTP, 1985).

Although not routinely used, biological markers or biomarkers of exposure could theoretically improve the exposure assessment process and, thereby, improve the overall risk assessment of neurotoxicants. Exposure biomarkers may include either the quantitation of exogenous agents or the

complex of endogenous substances and exogenous agents within the system (Committee on Biological Markers, 1987). A limited number of examples of biomarkers of exposure have been reviewed by Slikker (1991) and include blood or dentine lead concentrations (Needleman, 1987), cerebrospinal fluid concentrations of dopamine metabolites following MPTP administration (Kopin and Markey, 1988), cerebrospinal fluid concentrations of a serotonin metabolite following MDMA exposure (Ricaurte et al., 1986), and serum esterase concentrations following organophosphate exposure (Levine et al., 1986). The use of muscarinic receptor binding in peripheral plasma lymphocytes has also been described as a potential biomarker of exposure for the organophosphates (Costa et al., 1990). These examples suggest that biomarkers of exposure are available for some agents, but more effort will be required to demonstrate that these biomarkers can routinely be used to improve the exposure assessment process.

5.2.4. Risk Characterization

The final step of the risk assessment process combines the hazard identification, the dose-response assessment, and the exposure assessment to produce the characterization of risk. As previously stated, the current practice is to divide the NOAEL by the appropriate safety factor to obtain the RfD. The magnitudes of the safety factors used to determine RfDs [interspecies extrapolation (10), intraspecies extrapolation (10), and acute vs. chronic exposure (10) = 1000] are based more on conservative estimates than on actual data (Sheehan et al., 1989; McMillan, 1987) and have been questioned for empirical reasons (Gaylor and Slikker, 1990). Uncertainty factors may be decreased as more data become available. Modifying factors are also employed under certain circumstances to account for the completeness of data sets. Along with this RfD numerical value, any uncertainties and assumptions inherent in the risk assessment should also be stated (OTA, 1990). Although the RfD provides a single numerical value, it does not provide information concerning the uncertainty of this number nor does the RfD approach attempt to estimate the potential risk as a function of dose or consider the potential risk at the NOAEL. The risk at the NOAEL generally is greater than zero and has been estimated to be as high as about 5 percent (Crump, 1984; Gaylor, 1989). Concern has been expressed that the application of the

RfD approach to all neurotoxicants is unlikely to be biologically defensible in light of mechanistic data (NRC, 1992). Several other quantitative risk assessment procedures have recently emerged as alternatives to the RfD approach (Kimmel and Gaylor, 1988).

Quantitative risk assessment may be defined as a data-based process that uses dose-response information and measurements of human exposure to arrive at estimates of risk. Assumptions are required to extrapolate results from high to low doses, to extrapolate from animal results to humans, and to extrapolate across different routes and durations of exposure.

In a step toward quantitative risk assessment, Crump (1984) suggested the use of a benchmark dose defined as "a statistical lower confidence limit corresponding to a small increase in effect over the background level." The benchmark dose is determined with a mathematical model and is less affected by the particular shape of the dose-response curve. Although the benchmark approach avoids several problems inherent in the RfD approach (e.g., lack of precision in defining the LOAEL; Kimmel, 1990), the same final step of dividing by arbitrary safety factors is obligatory.

Another approach to quantitative risk assessment is the statistical or curve-fitting approach. If quantal information concerning the proportion of response at a given dose is available but mechanistic information is lacking, statistical models can be used to fit population data (Wyzga, 1990). This approach has been used to fit various models to data of lead toxicity. The data were sufficient to allow discrimination of several models in terms of goodness of fit; the nerve-conduction velocity data from children exposed to environmental lead as a function of blood lead concentration fit a "hockey-stick" type dose-response curve rather than a logistic or quadratic model (Schwartz et al., 1988). These statistical approaches not only provide a method to extrapolate data to lower exposure conditions but also can provide circumstantial evidence to support a proposed mechanism of action.

The development of quantitative risk assessment approaches depends, in part, on the availability of information on the mechanism of action and pharmacokinetics of the agent in question. In the development of a biologically based, dose-response model for MDMA neurotoxicity, Slikker and Gaylor (1990) considered several factors, including the pharmacokinetics of the parent chemical, the target tissue concentrations of the parent chemical or

its bioactivated proximate toxicant, the uptake kinetics of the parent chemical or metabolite into the target cell and membrane interactions, and the interaction of the chemical or metabolite with presumed receptor site(s). Because these theoretical factors contain a saturable step due to limited amounts of required enzyme, reuptake, or receptor site(s), a nonlinear, saturable dose-response curve was predicted. In this case of neurochemical effects of MDMA in the rodent, saturation mechanisms were hypothesized and indeed saturation curves provided relatively good fits to the experimental results. The conclusion was that use of dose-response models based on plausible biological mechanisms provide more validity to prediction than purely empirical models. Concomitant with attempts to develop quantitative risk assessment procedures, it is imperative that regulatory policy or risk management procedures also be developed to use appropriately the type of data generated by quantitative risk assessment. However, until alternative risk assessment procedures have been validated, the available RfD approach with its limitations will most likely continue to be used.

5.3. Generic Assumptions and Uncertainty Reduction

The purpose of risk assessment is to determine the risk associated with human exposure to a hazard. The quality of the data from toxicological studies differs. In the case of therapeutic products where human effects information is available, risk assessments rely primarily on the result of controlled clinical trials. Even when clinical trial data are available, however, conducting a risk assessment is complicated by many uncertainties. In the face of these uncertainties, conservative assumptions are usually made at several steps in the risk assessment process. For example, unless adequate clinical data are available, the most sensitive experimental species is frequently used. While conservative assumptions may lead to a risk assessment that adequately protects the human population, this may result in an increased financial burden on the public (e.g., manufacturing costs or loss of jobs); even then it is impossible to be certain that the total population will be protected. Conversely, errors leading to allowable exposure levels that are too high reduce the safety margin for human health and increase health care costs. Thus, there are compelling public health and economic reasons to obtain more precise risk assessments; all assumptions cannot be completely

eliminated, but the degree of uncertainty associated with certain specific assumptions can at least be reduced (Sheehan et al., 1989).

Risk assessment for neurotoxicity shares many common features with other noncancer toxicities such as developmental toxicity and immunotoxicity. As such, there are several generic assumptions that apply to all traditional, noncancer endpoint risk assessment procedures (Table 5-1).

TABLE 5-1.—GENERAL ASSUMPTIONS THAT UNDERLIE TRADITIONAL RISK ASSESSMENTS^{a,b}

1. A threshold dose exists for noncancer endpoints.
2. NOAEL/LOAEL uncertainty- or safety-factor approaches are reasonable.
3. Variability in the toxic response to the chemical exposure is not due to a heterogeneous population response.
4. Average dose or total dose is a reasonable measure of exposure when doses are not equivalent in time, rate, or route of administration and the average (or total) dose is proportional to adverse effect.
5. Structure-activity correlations can be used to predict human toxicity.
6. The mechanism of action is the same at all doses for all species.

^a This is not intended to be an exhaustive list.

^b Modified from Sheehan et al., 1989.

One approach to reducing some of the uncertainties is to critically define and examine the assumptions made in the risk assessment process. Several of the more generic of these assumptions are listed in Table 5-1. Despite their diversity, these assumptions share the attribute of being partially replaceable by factual information. If, for example, the assumption of 100 percent absorption of a toxicant from a contaminated food source is replaced by data demonstrating that 90 percent of the toxicant is not biologically available under human exposure conditions, then a revised risk assessment could allow a 10-fold greater exposure from that source; i.e., the former risk assessment was too conservative by a factor of 10. As another example, many risk assessments employ data from two species.

If experimental animals and humans absorb or metabolize the same fraction of a dose, the potency estimate would not change when extrapolating from animals to humans. Therefore, it is necessary to have information on both human and animal rates before changes in potency estimates are made. If a toxicant acts via a reactive intermediate and humans produce 10-fold more of

the intermediate than either of the test species under similar conditions, then allowable human exposure should be decreased 10-fold (i.e., the allowable exposure levels are 10-fold too high) or an increased danger to human health exists. These findings could then replace the "most sensitive species" principle with facts concerning relevant human exposure and susceptibility. In these examples, the identification of the assumption helps define research needs or knowledge gaps (Sheehan et al., 1989).

In general, the knowledge gaps are many and complex, but some can be filled with practical solutions. The combination of ample dose-response data and a quantitative risk assessment process can eliminate assumptions 1 (existence of a threshold) and 2 (reasonableness of safety factors) of the six generic assumptions (Table 5-1). The uncertainty of assumption 4 (exposure comparisons) could be at least reduced with the proper application of appropriate pharmacokinetic data. Likewise, the uncertainty of generic assumption 3 (variability of heterogeneous populations) can theoretically be reduced with the use of biomarkers of exposure and biomarkers of effect, to more accurately define the relationship between exposure and biological effect in a large population.

Many assumptions remain, however, and uncertainty reduction by filling knowledge gaps will ultimately require greater understanding of biological mechanisms underlying neurotoxicity. A single risk assessment model may not be adequate for all conditions of exposure, for all endpoints, or for all agents. Risk assessment models of the future may well include biomarkers of both effect and exposure as well as biologically based mechanistic considerations derived from both epidemiologic and experimental test system data.

6. General Summary

It is now generally accepted that some chemicals, including industrial agents, pesticides, therapeutic agents, drugs of abuse, food-related chemicals, and cosmetic ingredients, can have adverse effects on the structure and function of the nervous system. It has recently been proposed that exposure to neurotoxicants might also be associated with Parkinsonism and Alzheimer's disease. Several Federal agencies have initiated research programs in neurotoxicology, developed neurotoxicology testing guidelines, and used neurotoxic endpoints to regulate chemicals in the environment and workplace.

The scientific basis for identifying and characterizing chemical-induced neurotoxicity has advanced rapidly during the last several years. The manifestation of neurotoxicity depends on the relationship between exposure (applied dose) and the dose at the site of toxic action (delivered or target dose) and response. Chemical-induced changes in the structure or function of the nervous system at the cellular or molecular level can be observed as alterations in sensory, motor, or cognitive function at the level of the whole organism. Several important features about the nervous system make it particularly vulnerable to chemical insult, including differential susceptibilities at different stages of maturation, the presence of blood brain and nerve barriers that may be the target of toxic action, high metabolic rate, and limited regenerative capability following damage.

Methods devised to detect and quantify agent-induced changes in nervous system function in humans include clinical evaluations and neurotoxicity testing methods such as neurobehavioral, neurophysiological, neurochemical, imaging, and self-reporting procedures. Experimental approaches used in human neurotoxicology include epidemiological studies and, to a limited extent, human laboratory exposure studies. There are several important unresolved issues in human neurotoxicology, including the development of commonly accepted risk assessment criteria and animal-to-human extrapolation.

It is generally assumed that if physical or chemical-induced neurotoxicity is observed in animal models, then neurotoxicity will be produced in humans. Considerable research has been performed to demonstrate the validity of many animal models in an experimental context and to show predictive validity. Methods in animal neurotoxicology are frequently used in a tier-testing framework with simpler, more cost-effective tests to screen or identify neurotoxic potential. In hazard identification, the presence of neurotoxicity at the first tier is used to make decisions about subsequent development of a chemical or about the need to conduct additional experiments to define the level at which neurotoxicity will be observed. A number of methods have been devised for studies in animal neurotoxicology, including neurobehavioral, neurophysiological, neurochemical, and neuroanatomical techniques. It is known that the neuroendocrine system may be affected adversely by

neurotoxicants and that there are populations that are differentially vulnerable to neurotoxic agents. Considerable research is in progress to employ structure-activity relationships to predict neurotoxicity and newly developed *in vitro* procedures are being used to augment or complement currently existing *in vivo* approaches.

Principles of risk assessment for neurotoxicity are evolving rapidly. At the present time, neurotoxicity risk assessment is generally limited to qualitative hazard identification. Neurotoxicological risk assessments have been generally based on a no observed adverse effect level and uncertainty factors. As with other noncancer endpoints, there is a need to consider more information about the shape of the dose-response curve and mechanisms of effect in quantitative neurotoxicology risk assessment. Research is needed to develop dose-response models that incorporate biologic information and mechanistic hypotheses into quantitative extrapolation of dose-response relationships across species and from high to low dose exposures.

7. References

- Abou-Donia MB. Organophosphorus ester-induced delayed neurotoxicity. *Ann Rev Pharmacol Toxicol* 1981; 21:511-548.
- Abou-Donia MB. Toxicokinetics and metabolism of delayed neurotoxic organophosphorus esters. *Neurotoxicology* 1983; 4:113-130.
- Aibara K. Introduction to the Diagnosis of Mycotoxicosis. In: Richards JL, Thurston JR, eds. *Diagnosis of Mycotoxicoses*. Dordrecht, Netherlands: Martinus Nijhoff Publishers, 1986:3-8.
- Altmann J, Schardt H, Wiegand H. Selective effects of acute repeated solvent exposure on the visual system. *Arbete och Halsa* 1991; 35:67-69.
- Andersen ME, Clewell HJ, Gargas ML, MacNaughton MG, Reitz RH, Nolan RJ, McKenna MJ. Physiologically based pharmacokinetic modeling with dichloromethane, its metabolite, carbon monoxide, and blood carboxyhemoglobin in rats and humans. *Toxicol Appl Pharmacol* 1991; 108:14-27.
- Anderson-Brown T, Slotkin TA, Seidler FJ. Cocaine acutely inhibits DNA synthesis in developing rat brain regions: evidence for direct actions. *Brain Res* 1990; 537:197-202.
- Anger WK. Neurobehavioral testing of chemicals; impact on recommended standard. *Neurobehav Toxicol Teratol* 1984; 6:147-153.
- Anger WK. Worksite behavioral research: results, sensitive methods, test batteries and the transition from laboratory data to human health. *Neurotoxicology* 1990a; 11:629-720.
- Anger WK. Human neurobehavioral toxicology testing. In: Russell RW, Flattau PE, Pope AM, eds. *Behavioral Measures of*

- Neurotoxicity. Washington, DC: National Academy Press, 1990b.
- Anger WK. Animal test systems to study behavioral dysfunctions of neurodegenerative disorders. *Neurotoxicology* 1991; 12:403-414.
- Anger WK, Setzer JV. Effects of oral and intramuscular carbaryl administrations on repeated chain acquisition in monkeys. *J Toxicol Environ Health* 1979; 5:793-808.
- Annau Z, Eccles CU. Prenatal exposure. In: Annau A, ed. *Neurobehavioral Toxicology*. Baltimore: Johns Hopkins University Press, 1986:153-169.
- Atterwill CK, Walum E. Neurotoxicology in vitro: model systems and practical applications. *Toxic In Vitro* 1989; 3:159-161.
- Bacon CW, Bennett RM, Hinton DM. Scanning electron microscopy of Fusarium moniliforme within asymptomatic corn kernels and kernels associated with leukoencephalomalacia. *Plant Disease* 1992; 76:144-148.
- Baker EL, Letz RE, Fidler AT, Shalat S, Plantamura D, Lyndon M. A computer based neurobehavioral evaluation system for occupational and environmental epidemiology: methodology and validation studies. *Neurobehav Toxicol Teratol* 1985; 7:369-377.
- Barnes DG, Dourson M. Reference dose (RfD): description and use in health risk assessments. *Regul Toxicol Pharmacol* 1988; 8:471-486.
- Beaumont JG. Neurobehavioral tests: problems, potential, and prospects. In: Russell RW, Flatau PE, Pope AM, eds. *Behavioral Measures of Neurotoxicity*. Washington, DC: National Academy Press, 1990.
- Bell, L.R., Millers, C. and Schwartz, G.E. An olfactory-limbic model of multiple chemical sensitivity syndrome: Possible relationships to kindling and affective spectrum disorders. *Biol. Psychiat.* 1992; 32:218-242.
- Bellinger D, Leviton A, Waterneaux C, Needleman H, Rabinowitz M. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med* 1987; 316:1037-1043.
- Benignus, V. Importance of experimenter-blind procedure in neurotoxicology. *Neurotoxicol. Teratol.* 1993; 15:45-49.
- Berde B, Schield HO. Ergot alkaloids and related compounds. In: *Handbook of Experimental Pharmacology*. Berlin, Heidelberg, New York: Springer-Verlag, 1978:49.
- Bhattacharyya TK, Dayal VS. Ototoxicity and noise-drug interaction. *J Otolaryngol* 1984; 13:361-366.
- Bidstrup PL. Toxicity of Mercury and Its Compounds. Amsterdam: Elsevier Scientific Publishing Company, 1964.
- Boettcher FA, Henderson D, Gratton MA, Danielson RW, Byrne CD. Synergistic interactions of noise and other ototraumatic agents. *Ear Hear* 1987; 8:192-212.
- Bondy SC. Special considerations for neurotoxicological research. *CRC Crit Rev Toxicol* 1985; 14:381-402.
- Bondy SC. The biochemical evaluation of neurotoxic damage. *Fund Appl Toxicol* 1986; 6:208-215.
- Bove FJ. The Story of Ergot. Basel, Switzerland: S. Karger AG, 1970.
- Bowyer JF, Tank AW, Newport GD, Slikker W, Ali SF, Holson RR. The influence of environmental temperature on the transient levels of methamphetamine on dopamine levels and dopamine release in rat striatum. *J Pharmacol Exp Ther* 1992, in press.
- Boyce S, Kelly E, Reavill C, Jenner P, Marsen CD. Repeated administration of N-methyl-4-phenyl-1,2,5,6-tetra-hydropyridine to rats is not toxic to striatal dopamine neurons. *Biochem Pharmacol* 1984; 33:1747-1752.
- Brady LS, Barrett JE. Drug-behavior interaction history: modification of the effects of morphine on punished behavior. *J Exp Anal Behav* 1986; 45:221-228.
- Calne DB, Eisen A, McGeer E, Spencer PS. Alzheimer's disease, Parkinson's disease, and motoneuron disease: a biotrophic interaction between ageing and environment? *Lancet* 1986; II(8515):1067-1070.
- Cannon SB, Veazey JM, Jackson RS, Burse VW, Hayes C, Straub WE, Landrigan PJ, Liddle JA. Epidemic kepone poisoning in chemical workers. *Am J Epidemiol* 1978; 107:529-537.
- Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychol Bull* 1959; 56:81-91.
- Cassells DAK, Dodds EC. Tetra-ethyl lead poisoning. *Brit Med J* 1946; 2:4479-4483.
- Cassitto MG, Camerino D, Hanninen H, Anger WK. International collaboration to evaluate the WHO neurobehavioral core test battery. In: Johnson B, Anger WK, Durao A, Xintaras C, eds. *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*. Chelsea: Lewis Publishers, 1990.
- Cavanagh JB. The toxic effects of tri-ortho-cresyl phosphate on the nervous system: an experimental study on hens. *J Neurol Neurosurg Psychiat* 1954; 17:163-172.
- Centers for Disease Control (CDC). Preventing lead poisoning in young children. U.S. Department of Health and Human Services, Centers for Disease Control, Atlanta, GA, 1991.
- Centers for Disease Control (CDC). Prevention of leading work-related diseases and injuries. *MMWR*, 1986; 35(8).
- Chang LW. Mercury. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:508-526.
- Chiba S, Ando K. Effects of chronic administration of kanamycin on conditioned suppression to auditory stimulus in rats. *Jpn J Pharmacol* 1976; 26:41-426.
- Choi DW. Glutamate neurotoxicity and diseases of the nervous system. *Neuron* 1988; 1:623-634.
- Committee on Biological Markers of the National Research Council. Biological markers in environmental health research. *Environ Health Perspect* 1987; 74:3-9.
- Cone JE, Reeve GR, Landrigan PJ. Clinical and epidemiological studies. In: Tardiff RG, Rodricks JV, eds. *Toxic Substances and Human Risk*. New York: Plenum Press, 1987.
- Cook DG, Fahn S, Brait KA. Chronic manganese intoxication. *Arch Neurol* 1974; 30:59-71.
- Cory-Slechta DA. Behavioral measures of neurotoxicity. *Neurotoxicology* 1989; 10:271-296.
- Cory-Slechta DA. Bridging experimental animal and human behavioral toxicology studies. In: Russell RW, Flatau PE, Pope AM, eds. *Behavioral Measures of Neurotoxicity*. Washington, DC: National Academy Press, 1990.
- Costa LG. Interactions of neurotoxicants with neurotransmitter systems. *Toxicology* 1988; 49:359-366.
- Costa LG, Kaylor G, Murphy SD. In vitro and in vivo modulation of cholinergic muscarinic receptors in rat lymphocytes and brain by cholinergic agents. *Int J Immunopharmacol* 1990; 8:1267-75.
- Creason JP. Data evaluation and statistical analysis of functional observational battery data using a linear models approach. *J Am Coll Toxicol* 1989; 8:157-169.
- Crofton KM. Reflex modification and the detection of toxicant-induced auditory dysfunction. *Neurotoxicol Teratol* 1990; 12:461-468.
- Crook T, Ferris S, Bartus R, eds. *Assessment in Geriatric Psychopharmacology*. New Canaan, NY: Mark Powley Associates, 1983.
- Crump KS. A new method for determining allowable daily intakes. *Fund Appl Toxicol* 1984; 4:854-871.
- Cushman IM. Maternal behavior and perinatal risks: alcohol, smoking, and drugs. *Ann Rev Pub Health* 1981; 2:201-218.
- Damstra T, Bondy SC. The current status and future of biochemical assays for neurotoxicity. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:820-833.
- Davies PW. The action potential. In: Mountcastle VB, ed. *Medical Physiology*. 12th edition. St. Louis: C.V. Mosby, 1968:1094-1120.
- Davis CS, Richardson RJ. Organophosphorous compounds. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:527-544.
- Denny-Brown D, Dawson DM, Tyler HR. *Handbook of Neurological Examination and Case Recording* (3rd ed). Cambridge: Harvard University Press, 1982.
- Dews PB. On the assessment of risk. In: Krasnegor N, Gray J, Thompson T, eds. *Developmental Behavioral Pharmacology*. Hillsdale, NJ: Lawrence Erlbaum Associates, 1986:53-65.
- Dick, RB. Short duration exposure to organic solvents: the relationship between neurobehavioral test results and other indicators. *Neurotoxicol. Teratol.* 1988; 10:35-50.
- Dick RB, Johnson BL. Human experimental studies. In: Annau Z, ed. *Neurobehavioral Toxicology*. Baltimore: Johns Hopkins University Press, 1986.
- Dick RB, Bhattacharya A, Shukla R. Use of a computerized postural sway measurement system for neurobehavioral toxicology. *Neurotoxicol Teratol* 1990; 12:1-6.

- Dick, RB, Krieg, EF, Setzer, J, Taylor, B. Neurobehavioral effects from acute exposure to methyl isobutyl ketone and methyl ethyl ketone. *Fund. Appl. Toxicol.* 1992; 19:453-473.
- Domjan M, Burkhard B. *The Principles of Learning and Memory*. Monterey, CA: Cole, 1986.
- Dourson ML, Stara JF. Regulatory history and experimental support of uncertainty (safety) factors. *Regul Toxicol Pharmacol* 1983; 3:224-238.
- Dyer RS. Macrophysiological assessment of organometal neurotoxicity. In: Tilson H, Sparber SB, eds. *Neurotoxicants and Neurobiological Function*. New York: Wiley, 1987:137-184.
- Dyer RS, Howell WE. Triethyltin: ambient temperature alters visual system toxicity. *Neurobehav Toxicol Teratol* 1982; 4:267-271.
- Eccles CU. EEG correlates of neurotoxicity. *Neurotoxicol Teratol* 1988; 10:423-428.
- Eckerman DA, Bushnell PJ. The neurotoxicology of cognition: Attention, learning and memory. In: Tilson H, Mitchell CL, eds. *Neurotoxicology*. New York: Raven Press, 1992:213-270.
- Eckerman DA, Carroll JB, Forre D, Gullion CM, Lansman M, Long ER, Waller MB, Wallsten TS. An approach to brief field testing for neurotoxicity. *Neurobehav Toxicol Teratol* 1985; 7:387-393.
- Ecobichon DJ, Joy RM. *Pesticides and Neurologic Disease*. Boca Raton: CRC Press, 1982.
- Fechter LD, Young IS. Discrimination of auditory from non-auditory toxicity by reflex modification audiometry: effects of triethyltin. *Toxicol Appl Pharmacol* 1983; 70:216-227.
- Festing MFW. Genetic factors in neurotoxicology and neuropharmacology: a critical evaluation of the use of genetics as a research tool. *Experientia* 1991; 12:1877-1888.
- Fisher F. Neurotoxicology and government regulation of chemicals in the United States. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:874-882.
- Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on carcinogenesis report on cancer testing in the safety evaluation of food additives and pesticides. *Toxicol Appl Pharmacol* 1971; 20:419-438.
- Fowler SC. Force and duration of operant response and dependent variables in behavioral pharmacology. In: Thompson T, Dews PB, eds. *Advances in Behavioral Pharmacology*. New York: Erlbaum, 1987.
- Freed DM, Kandel E. Long-term occupational exposure and the diagnosis of dementia. *Neurotoxicology* 1988; 9:391-400.
- Friedel RO. Pharmacokinetics in the geropsychiatric patient. In: Lipton, M., Usdin, E., Killam, K., eds. *Psychopharmacology: A Generation of Progress*. New York: Raven Press, 1978.
- Friedlander BR, Hearn HT. Epidemiologic considerations in studying neurotoxic disease. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:650-662.
- Fullerton PM. Electrophysiological and histological observations on peripheral nerves in acrylamide poisoning in man. *J Neurol Neurosurg Psychiatr* 1969; 32:186.
- Gad SC. Principles of screening in toxicology with special emphasis on applications to neurotoxicology. *J Am Coll Toxicol* 1989; 8:21-27.
- Gallagher RT, Hawkes AD, Steyn PS, Villegas R. Tremorgenic neurotoxins from perennial ryegrass causing ryegrass staggers disorders of livestock: structure and elucidation of Lolitrem. *Chem Soc Chem Comm* 1984; 18:614-616.
- Gaylor DW. Quantitative risk analysis for quantal reproductive and developmental effects. *Environ Health Perspect* 1989; 79:243-246.
- Gaylor DW, Slikker W Jr. Risk assessment for neurotoxic effects. *Neurotoxicology* 1990; 11:211-218.
- Gaylor D, Slikker W Jr. Risk assessment for neurotoxicants. In: Tilson H, Mitchell C, eds. *Neurotoxicology*. New York: Raven Press, 1992:331-343.
- Glowa JR, Dews PB. Behavioral toxicology of volatile organic solvents. IV. Comparison of the behavioral effects of acetone, methyl ethyl ketone, ethyl acetate, carbon disulfide, and toluene on the responding of mice. *J Am Coll Toxicol* 1987; 6:461-469.
- Glowa J, DeWeese J, Natale ME, Holland JJ. Behavioral toxicology of volatile organic solvents. I. Methods: acute effects. *J Am Coll Toxicol* 1983; 2:175-185.
- Goldberg AM, Frazier JM. Alternatives to animals in toxicity testing. *Sci Amer* 1989; 261:24-30.
- Goldstein MK, Stein GH. Ambulatory activity in chronic disease. In: Tryon WH, ed. *Behavioral Assessment in Behavioral Medicine*. New York: Springer Publishing Co., 1985:160-162.
- Griffin JW. Basic pathologic processes in the nervous system. *Toxicologic Pathology* 1990; 18:83-88.
- Hagstadius, S, Orbaek, P, Risberg, J, Lindgren, M. Regional cerebral blood flow at the time of diagnosis of chronic toxic encephalopathy induced by organic solvent exposure and after the cessation of exposure. *Scand. J. Work Environ. Health*, 1989; 15:130-135.
- Hammerschlag R, Brady S. Axonal transport and the neuronal cytoskeleton. In: Siegel GJ, Agranoff BW, Albers RW, Molinoff PB, eds. *Basic Neurochemistry*. New York: Raven Press, 1989:457-473.
- Hanninen H. Methods in behavioral toxicology: current test batteries and need for development. In: Russell RW, Flatau PE, Pope AM, eds. *Behavioral Measures of Neurotoxicity*. Washington, DC: National Academy Press, 1990.
- Hanninen H, Mantere P, Hernberg S, Seppäläinen AM, Kock B. Subjective symptoms in low-level exposure to lead. *Neurotoxicology* 1979; 1:333-347.
- Hattis D, Shapiro K. Analysis of dose/time/response relationships for chronic toxic effects: the case of acrylamide. *Neurotoxicology* 1990; 11:219-236.
- HAZDAT. ATSDR Database. Agency for Toxic Substances and Disease Registry. Atlanta, GA, 1992.
- Hoikkila RE, Hess A, Duvoisin RC. Dopaminergic neurotoxicity of methyl-4-phenyl-1,2,5,6-tetrahydropyridine in mice. *Science* 1984; 224:1451-1453.
- Heise GA. Behavioral methods for measuring effects of drugs on learning and memory in animals. *Med Res Rev* 1984; 4:535-558.
- Hill RM, Tennyson LM. Maternal drug therapy: effect on fetal and neonatal growth and neurobehavior. *Neurotoxicology* 1986; 7:121-140.
- Hjelm, EW, Hagberg, M, Iregren, A, Lof, A. Exposure to methyl isobutyl ketone: toxicants and occurrence of irritative and CNS symptoms in man. *Int. Arch. Occup. Environ. Health*, 1990; 62:19-26.
- Hooisma J, Emmen HH, Kulig BM, Muijsers H, Poortvliet D, Letz R. Factor analysis of tests from the neurobehavioral evaluation system and the WHO neurobehavioral core test battery. In: Johnson B, Anger WK, Durao A, Xintaras C, eds. *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*. Chelsea: Lewis Publishers, 1990.
- Horvath M, Frantik E. Quantitative interpretation of experimental toxicological data: the use of reference substances. In: Horvath M, ed. *Adverse Effects of Environmental Chemicals and Psychotropic Drugs*. Amsterdam: Elsevier, 1973:11-21.
- Hruska RE, Kennedy S, Silbergeld EK. Quantitative aspects of normal locomotion in rats. *Life Sci* 1979; 25:171-179.
- Hutchings DE, Fico TA, Dow-Edwards DL. Prenatal cocaine: maternal toxicity, fetal effects and locomotor activity of rat offspring. *Neurotoxicol Teratol* 1989; 11:65-69.
- Iregren A, Gamberale F, Kjellberg A. A microcomputer-based behavioral testing system. In: *Neurobehavioral Methods in Occupational and Environmental Health*. Copenhagen: World Health Organization, 1985.
- Joffe JM, Soyka LF. Effects of drug exposure on male reproductive processes and progeny. *Period Biol* 1981; 83:351-362.
- Johnson MK. Organophosphates and delayed neuropathy—Is NTE alive and well? *Toxicol Appl Pharmacol* 1990; 102:385-399.
- Johnson BL. Prevention of neurotoxic illness in working populations. New York: Wiley, 1987.
- Johnson BL, Boyd J, Burg JR, Lee ST, Xintaras C, Albright BE. Effects on the peripheral nervous system of workers exposed to carbon disulfide. *Neurotoxicology* 1983; 4:53-66.
- Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 1973; 2:999-1001.
- Katzman R. Blood-brain-CSF barriers. In: Siegel GJ, ed. *Basic Neurochemistry*. Boston: Little, Brown and Company, 1976:414-423.
- Kimmel CA. Current status of behavioral teratology: science and regulation. *CRC Critical Reviews in Toxicology* 1984; 10:1-10.
- Kimmel CA. Quantitative approaches to human risk assessment for noncancer health effects. *Neurotoxicology* 1990; 11:189-193.
- Kimmel CA, Gaylor DW. Issues in qualitative and quantitative risk analysis for

- developmental toxicology. *Risk Analysis* 1988; 8:15-20.
- Kimmel CA, Rees DC, Francis EZ. Qualitative and quantitative comparability of human and animal developmental neurotoxicology. *Teratology* 1990; 12:175-292.
- Klaassen CD. Absorption, distribution, and excretion of toxicants. In: Doull J, Klaassen CD, Amdur M, eds. *Toxicology: The Basic Science of Poisonings*. New York: MacMillan, 1980:28-55.
- Kopin IJ, Markey SP. MPTP toxicity: implications for research in Parkinson's disease. *Ann Rev Neurosci* 1988; 11:91-96.
- Krinke GJ. Neuropathologic screening in rodent and other species. *J Am Coll Toxicol* 1989; 8:141-155.
- Kurata H. Mycotoxins and mycotoxicoses: overview. In: Pohland AE, Dowell VR Jr, Richards JL, eds. *Microbial Toxins in Foods and Feeds, Cellular and Molecular Modes of Action*. New York: Plenum Press, 1990:249-259.
- Langston JW, Ballard P, Tetrud JW, Irwin L. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 1983; 219:979-980.
- Last JM. Epidemiology and health information. In: Last JM, ed. *Maxcy-Rosenau Public Health and Preventive Medicine*. New York: Appleton-Century-Crofts, 1986.
- Letz R. The neurobehavioral evaluation system: an international effort. In: Johnson B, Anger WK, Durao A, Xintaras C, eds. *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*. Chelsea: Lewis Publishers, 1990.
- Levine MS, Fox NL, Thompson B, Taylor W, Darlington AC, Van Der Hoeden J, Emmett EA, Rutten W. Inhibition of esterase activity and an undercounting of circulating monocytes in a population of production workers. *J Occup Med* 1986; 28:207-211.
- Liang Y-X, Chen Z-Q, Sun R-K, Fan Y-F, Yu J-H. Application of the WHO neurobehavioral core test battery and other neurobehavioral screening methods. In: Johnson B, Anger WK, Durao A, Xintaras C, eds. *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*. Chelsea: Lewis Publishers, 1990.
- Lim DJ. Effects of noise and ototoxic drugs at the cellular level in the cochlea: a review. *Am J Otolaryngol* 1986; 7:73-99.
- Little RE, Anderson KW, Ervin CH, Worthington-Roberts B, Clarren SK. Maternal alcohol use during breast-feeding and infant mental and motor development at one year. *N Engl J Med* 1989; 321:425-430.
- Lowndes HE, Baker T. Toxic site of action in distal axonopathies. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:193-205.
- MacPhail RC. Effects of pesticides on schedule-controlled behavior. In: Seiden LS, Balster RL, eds. *Behavioral Pharmacology: The Current Status*. New York: Alan R. Liss, 1985:519-535.
- MacPhail RC. Environmental modulation of neurotoxicity. In: Russell RW, Flattau PE, Pope AM, eds. *Behavioral Measures of Neurotoxicity*. Washington, DC: National Academy Press, 1990.
- MacPhail RC, Crofton KM, Reiter LW. Use of environmental challenges in behavioral toxicology. *Fed Proc* 1983; 42:3196-3200.
- MacPhail RC, Peele DB, Crofton KM. Motor activity and screening for neurotoxicity. *J Am Coll Toxicol* 1989; 8:117-125.
- Mailman RB. Mechanisms of CNS injury in behavioral dysfunction. *Neurotoxicol Teratol* 1987; 9:417-426.
- Matthews HB, Dixon D, Herr DW, Tilson HA. Subchronic toxicity studies indicate that tris(2-chloroethyl)phosphate administration results in lesions in the rat hippocampus. *Toxicol Indust Health* 1990; 6:1-15.
- Mattsson JL, Albee RR. Sensory evoked potentials in neurotoxicology. *Neurotoxicol Teratol* 1988; 10:435-443.
- Maurissen JP. Quantitative sensory assessment in toxicology and occupational medicine: applications, theory and critical appraisal. *Toxicol Lett* 1988; 43:321-343.
- Maurissen JP, Weiss B, Davis HT. Somatosensory thresholds in monkeys exposed to acrylamide. *Toxicol Appl Pharmacol* 1983; 71:266-279.
- Mausner JS, Kramer S. *Epidemiology—An Introductory Text* (2nd ed). Philadelphia: W.B. Saunders Co., 1985.
- McMillan DE. Risk assessment for neurobehavioral toxicity. *Environ Health Perspect* 1987; 76:155-161.
- Merigan WH. Effects of toxicants on visual systems. *Neurobehav Toxicol* 1979; 1 (Suppl.):15-22.
- Morell P, Mailman RB. Selective and nonselective effects of organometals on brain neurochemistry. In: Tilson HA, Sparber SB, eds. *Neurotoxicants and Neurobiological Function: Effects of Organoheavy Metals*. New York: Wiley, 1987:201-230.
- Moser VC. Screening approaches to neurotoxicity: a functional observational battery. *J Am Coll Toxicol* 1989; 8:85-93.
- Moser VC. Approaches for assessing the validity of a functional observational battery. *Neurotoxicol Teratol* 1990; 12:483-488.
- Moser VC, McDaniel KL, Phillips PM. Rat strain and stock comparisons using a functional observational battery: baseline values and effects of amitraz. *Toxicol Appl Pharmacol* 1991; 108:267-283.
- National Institute for Occupational Safety and Health (NIOSH). NIOSH Recommendations for Occupational Safety and Health: Compendium of Policy Documents and Statement. DHHS Pub. No. 92-100, 1992.
- National Research Council, Committee on Toxicology. *Effects on behavior*. In: *Principles for Evaluating Chemicals in the Environment*. Washington, DC: National Academy of Sciences, 1975.
- National Research Council (NRC). *Risk Assessment in the Federal Government*. Washington, DC: National Academy Press, 1983.
- National Research Council (NRC). *Toxicity Testing: Strategies to Determine Needs and Priorities*. Washington, DC: National Academy of Sciences, 1984.
- National Research Council (NRC). *Environmental Neurotoxicology*. Washington, DC: National Academy Press, 1992.
- Needleman HL. Introduction: biomarkers in neurodevelopmental toxicology. *Environ Health Perspect* 1987; 74:149-152.
- Needleman HL. Lessons from the history of childhood bluntness for pediatric neurotoxicology. In: Johnson BL, Anger WK, Durao A, Xintaras C, eds. *Advances in Neurobehavioral Toxicology: Application in Experimental and Occupational Health*. Chelsea: Lewis Publishers, 1990:331-337.
- Needleman HL, Gunnoe CE, Leviton A. Deficits in psychologic and classroom performance of children with elevated blood lead levels. *N Engl J Med* 1979; 300:689-695.
- Nelson BK. Evidence for behavioral teratogenicity in humans. *J Appl Toxicol* 1991a; 11:33-37.
- Nelson BK. Selecting exposure parameters in developmental neurotoxicity assessments. *Neurotoxicol Teratol* 1991b; 13:569-573.
- Newland MC. Quantification of motor function in toxicology. *Toxicol Lett* 1988; 43:295-319.
- O'Callaghan JP. Neurotypic and gliotypic proteins as biochemical markers of neurotoxicity. *Neurotoxicol Teratol* 1988; 10:445-452.
- O'Donoghue JL. Screening for neurotoxicity using a neurologically based examination and neuropathology. *J Am Coll Toxicol* 1989; 8:97-116.
- Office of Science and Technology Policy (OST). *Chemical carcinogens: a review of the science and its associated principles*. Federal Register 1985:1-85.
- Office of Technology Assessment (OTA). *Neurotoxicity: identifying and controlling poisons of the nervous system*. U.S. Congress. Office of Technology Assessment (OTA-BA-436), Washington, DC: U.S. Government Printing Office, 1990.
- Otto DA, Hudnell HK. Electrophysiological systems for neurotoxicity field testing: PEARL II and alternatives. In: Johnson B, Anger WK, Durao A, Xintaras C, eds. *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*. Chelsea: Lewis Publishers, 1990.
- Otto DA, Hudnell HK. Problems in studying low level solvent mixtures. *Arbete och Halsa* 1991; 35:35-38.
- Overstreet DH. Pharmacological approaches to habituation of the acoustic startle response in rats. *Physiol Psychol* 1977; 5:230-238.
- Pardridge WM. Recent advances in blood-brain transport. *Ann Rev Pharmacol Toxicol* 1988; 28:25-39.
- Paule MG, Forrester TM, Maher MA, Cranmer JM, Allen RR. Monkey versus human performance in the NCTR operant test battery. *Neurotoxicol Teratol* 1990; 12:503-507.
- Paule MG, McMillan DE. Incremental repeated acquisition in the rat: acute effects of drugs. *Pharmacol Biochem Behav* 1984; 21:431-439.
- Pearson DT, Dietrich KN. The behavioral toxicology and teratology of childhood:

- models, methods, and implications for intervention. *Neurotoxicology* 1985; 6:165-182.
- Peele DB, Vincent A. Strategies for assessing learning and memory, 1978-1987: a comparison of behavioral toxicology, psychopharmacology and neurobiology. *Neurosci Biobehav Rev* 1989; 13:33-38.
- Perl TM, Bedard L, Kosatsky T, Hockin JC, Todd ECD, Remis RS. An outbreak of toxic encephalopathy caused by eating mussels contaminated with domoic acid. *N Engl J Med* 1990; 322:1775-1780.
- Peters, A, Palay, SL, Webster, H. def. *The Fine Structure of the Nervous System. Neurons and Their Supporting Cells*, 3rd Ed. New York: Oxford University Press, 1991.
- Piikivi L, Tolonen U. EEG findings in chloralkali workers subjected to low long term exposure to mercury vapor. *Br J Ind Med* 1989; 46:30-35.
- Politis MJ, Schaumburg HH, Spencer PS. Neurotoxicity of selected chemicals. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980: 613-630.
- Pryor G, Dickinson J, Howd RA, Robert CS. Transient cognitive deficits and high-frequency hearing loss in weanling rats exposed to toluene. *Neurobehav Toxicol Teratol* 1983; 5:53-57.
- Putz VR, Johnson BL, Setzer JV. A comparative study of the effects of carbon monoxide and methylene chloride on human performance. *J Environ Path Toxicol* 1979; 2:97-112.
- Raine CS. Neurocellular anatomy. In: Siegal GJ, Agranoff BW, Albers RW, Molinoff PB, eds. *Basic Neurochemistry*. New York: Raven Press, 1989:3-34.
- Rao BL, Husain A. Presence of cyclopiation acid in Kodo millet (*Paspalum scrobiculatum*) causing 'Kodua poisoning' in man and its production by associated fungi. *Mycopathologia* 1985; 89:177-180.
- Robert CS. Multisensory evoked potentials in experimental and applied neurotoxicology. *Neurobehav Toxicol Teratol* 1983; 5:659-671.
- Reiter LW. Neurotoxicology in regulatory and risk assessment. *Develop Pharmacol Therap* 1987; 10:354-368.
- Ricaurte GA, Delanney LE, Weiner SG, Irwin I, Langston JW. 5-Hydroxyindoleacetic acid in cerebrospinal fluid reflects serotonergic damage induced by 3,4-methylenedioxymethamphetamine in CNS of nonhuman primates. *Brain Res* 1986; 474:359-363.
- Rice DG. Quantification of operant behavior. *Toxicol Lett* 1988; 43:361-379.
- Riley AL, Tuck DL. Conditioned taste aversions: a behavioral index of toxicity. *Ann NY Acad Sci* 1985; 443:272-292.
- Riley EP, Vorhees CV, eds. *Handbook of Behavioral Teratology*. New York: Plenum Press, 1986.
- Rodier PM. Time of exposure and time of testing in developmental neurotoxicology. *Neurotoxicology* 1986; 7:69-76.
- Rodier P. Developmental neurotoxicology. *Toxicologic Pathol* 1990; 18:89-95.
- Russell RW. Essential roles for animal models in understanding human toxicities. *Neurosci Biobehav Rev* 1991; 15:7-11.
- Ryan CM, Morrow LA, Bromet EJ, Parkinson DK. Assessment of neuropsychological dysfunction in the workplace: normative data from the Pittsburgh Occupational Exposures Test Battery. *J Clin Exp Neuropsychol* 1987; 9:665-679.
- Salzman C. Antianxiety agents. In: Crook T, Cohen G, eds. *Physicians' Handbook on Psychotherapeutic Drug Use in the Aged*. New Canaan, NY: Mark Powley Associates, 1981.
- Schrot J, Thomas JR, Robertson RF. Temporal changes in repeated acquisition behavior after carbon monoxide exposure. *Neurobehav Toxicol Teratol* 1984; 6:23-28.
- Schwartz J, Landrigan PF, Feldman RG, Silbergeld EK, Baker EL, Von Lindern IH. Threshold effect in lead-induced peripheral neuropathy. *J Pediatr* 1988; 11:212-217.
- Seppalainen AM, Haltia M. Carbon disulfide. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:356-373.
- Seppalainen AM, Harkonen H. Neurophysiological findings among workers occupationally exposed to styrene. *Scand J Work Environ Health* 1976; 2:140.
- Sette WF, MacPhail RC. Qualitative and quantitative issues in assessment of neurotoxic effects. In: Tilson H, Mitchell C, eds. *Neurotoxicology*. New York: Raven Press, 1992:345-361.
- Sheehan DM, Young JF, Slikker W Jr, Gaylor DW, Mattison DR. Workshop on risk assessment in reproductive and developmental toxicology: addressing the assumptions and identifying the research needs. *Regulat Toxicol Pharmacol* 1989; 10:110-122.
- Silbergeld EK. Maternally mediated exposure of the fetus: in utero exposure to lead and other toxins. *Neurotoxicology* 1986; 7:557-568.
- Silbergeld EK. Developing formal risk assessment methods for neurotoxicants: an evaluation of the state of the art. In: Johnson BL, Anger WK, Durao A, Xintaras C, eds. *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*. Chelsea: Lewis, 1990:133-148.
- Sjogren B, Gustavsson P, Hogstedt C. Neuropsychiatric symptoms among welders exposed to neurotoxic metals. *Brit J Indust Med* 1990; 47:704-707.
- Slikker W Jr. Biomarkers of neurotoxicity: an overview. Recent advances on biomarker research. *Biomed Environ Sci* 1991; 4:192-196.
- Slikker W Jr, Gaylor DW. Biologically based dose-response model for neurotoxicity risk assessment. *Korean J Toxicol* 1990; 6:204-213.
- Slikker W Jr, Holson RR, Ali SF, Kolta MG, Paule MG, Scallet AC, McMillan DE, Bailey JR, Hong JS, Scalzo FM. Behavioral and neurochemical effects of orally administered MDMA in the rodent and nonhuman primate. *Neurotoxicology* 1989; 10:529-542.
- Smith MA, Grant LD, Sors AI, eds. *Lead Exposure and Child Development: An International Assessment*. Dordrecht, Netherlands: Kluwer Academic Publishers, 1989.
- Solomon PR, Pendlebury WW. A model systems approach to age-related memory disorders. *Neurotoxicology* 1988; 9:443-462.
- Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins Co, 1980.
- Spencer PS, Nunn PB, Hugon J, Ludolph AC, Ross SM, Roy DN, Robertson RC. Guam amyotrophic lateral sclerosis-Parkinsonism-dementia linked to a plant excitant neurotoxin. *Science* 1987; 237:517-522.
- Squibb, RE, Tilson, HA, Meyer, OA, Lamartiniere, CA. Neonatal exposure to monosodium glutamate alter the neurobehavioral performance of adult rats. *Neurotoxicology*, 1991; 2:471-484.
- Stanton ME, Spear LP. Comparability of endpoints across species in developmental neurotoxicity. *Neurotoxicol Teratol* 1990; 12:261-268.
- Stebbins WC, Coombs C. Behavioral assessment of ototoxicity in nonhuman primates. In: Weiss B, Laties VG, eds. *Behavioral Toxicology*. New York: Plenum Press, 1975.
- Sterman AB, Schaumburg HH. Neurotoxicity of selected drugs. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:593-612.
- Stewart RD, Fisher TN, Hosko R. Experimental human exposure to methylene chloride. *Arch Environ Health* 1972; 25:342-348.
- Strong MJ, Garruto RM. Potentiation in the neurotoxic induction of experimental chronic neurodegenerative disorders: n-butyl benzenesulfonamide and aluminum chloride. *Neurotoxicology* 1991; 12:415-426.
- Suzuki K. Special vulnerabilities of the developing nervous system to toxic substances. In: Spencer PS, Schaumburg HH, eds. *Experimental and Clinical Neurotoxicology*. Baltimore: Williams and Wilkins, 1980:48-61.
- Terrace HS. Errorless discrimination learning in the pigeon: Effects of chlorpromazine and imipramine. *Science* 1963; 140:318-319.
- Thompson FN Jr, Porter JK. Tall fescue toxicosis in cattle: could there be a public health problem. *Vet Human Toxicol* 1990; 32:51-57.
- Tilson HA, Cabe PA. Strategy for the assessment of neurobehavioral consequences of environmental factors. *Environ Health Perspect* 1978; 26:287-299.
- Tilson HA. Practical considerations in establishing valid and sensitive neurobehavioral test methods. *Zbl Bakt Hyg B* 1987; 185:10-15.
- Tilson HA. Screening for neurotoxicity: principles and practices. *J Am Coll Toxicol* 1989; 8:13-17.
- Tilson HA. Behavioral indices of neurotoxicity. *Toxicologic Pathology* 1990a; 18:96-104.
- Tilson HA. Neurotoxicology in the 1990s. *Neurotoxicol Teratol* 1990b; 12:293-300.
- Tilson HA, Mitchell CL. Neurotoxicants and adaptive responses of the nervous system. *Fed Proc* 1983; 42:3189-3190.

- Tilson HA, Mitchell CL. Neurobehavioral techniques to assess the effects of chemicals on the nervous system. *Ann Rev Pharmacol Toxicol* 1984; 24:25-50.
- Tilson HA, Moser VC. Comparison of screening approaches. *Neurotoxicology* 1992; 13:1-14.
- United States Environmental Protection Agency (U.S. EPA). Neurotoxicity Testing Guidelines. Springfield, VA: National Technical Information Service, 1991.
- Valciukas JA. Foundations of Environmental and Occupational Neurotoxicology. New York: Van Nostrand Reinhold, 1991.
- Veronesi B. The use of cell culture for evaluating neurotoxicity. In: Tilson HA, Mitchell CL, eds. New York: Raven Press, 1991:21-50.
- Veronesi B, Jones K, Pope C. The neurotoxicity of subchronic acetylcholinesterase (AChE) inhibition in rat hippocampus. *Toxicol Appl Pharmacol* 1990; 104:440-456.
- Verity MA, Sarafian TS, Guerra W, Ettinger A, Sharp J. Ionic modulation of triethyllead neurotoxicity in cerebellar granule cell culture. *Neurotoxicology* 1990; 11:415-426.
- Vorhees CV. Reliability, sensitivity and validity of indices of neurotoxicity. *Neurotoxicol Teratol* 1987; 9:445-464.
- Waddell, WJ. The science of toxicology and its relevance to MC5. *Reg. Toxicol. Pharmacol.* 1993; 18:13-22.
- Walker CH, Faustman WO, Fowler SC, Kazar DB. A multivariate analysis of some operant variables used in behavioral pharmacology. *Psychopharmacology* 1981; 74:182-186.
- Veiss B. Risk assessment: The insidious nature of neurotoxicity and the aging basis. *Neurotoxicology* 1990; 11:305-313.
- Villiamson AM. The influence of subject characteristics on the identification of acute effects of solvent exposure. *Arbete och Halsa* 1991; 35:14-18.
- Villis WD Jr, Grossman RG. Neurotransmission. In: Medical Neurobiology. St. Louis: C.V. Mosby, 1973:457.
- World Health Organization (WHO). Principles and Methods for the Assessment of Neurotoxicity Associated with Exposure to Chemicals. Environmental Health Criteria Document 60. Geneva: World Health Organization, 1986.
- Wyllie TD, Morehouse LC. Mycotoxic Fungi. Mycotoxins, Mycotoxicoses, An Encyclopedic Handbook. New York: Marcel Dekker, Inc., 1978, Vols. 1-3.
- Wyzga R. Towards quantitative risk assessment for neurotoxicity. *Neurotoxicology* 1990; 11:199-208.
- Yokel RA. Repeated systemic aluminum exposure effects on classical conditioning of the rabbit. *Neurobehav Toxicol Teratol* 1983; 5:41-46.
- Yokel RA, Provan SD, Meyer JJ, Campbell SR. Aluminum intoxication and the victim of Alzheimer's disease: similarities and differences. *Neurotoxicology* 1988; 9:429-442.
- Zenick H. Use of pharmacological challenge to disclose neurobehavioral deficits. *Fed Proc* 1983; 42:3191-3195.
- Prepared by
Working Party on Neurotoxicology
Subcommittee on Risk Assessment
Federal Coordinating Council on Science, Engineering, and Technology
Lawrence W. Reiter, USEPA, Chair
Hugh A. Tilson, USEPA, Executive Secretary
John Dougherty, NIOSH
G. Jean Harry, NIEHS
Carol J. Jones, OSHA
Suzanne McMaster, USEPA
William Slikker, NCTR/FDA
Thomas J. Sobotka, FDA
- Ad Hoc Interagency Committee on Neurotoxicology**
William Boyes, U.S. Environmental Protection Agency
Joy Cavagnaro, Food and Drug Administration
Selene Chou, Agency for Toxic Substances and Disease Registry
Murray Cohn, U.S. Consumer Product Safety Commission
Joseph F. Contrera, Food and Drug Administration
Miriam Davis, National Institute of Environmental Health Sciences, National Institutes of Health
Joseph DeGeorge, Food and Drug Administration
Robert Dick, National Institute for Occupational Safety and Health
John Dougherty, National Institute for Occupational Safety and Health
Lynda Erinoff, National Institute on Drug Abuse
Joseph P. Hanig, Food and Drug Administration
G. Jean Harry, National Institute of Environmental Health Sciences
David G. Hattan, Food and Drug Administration
Norman A. Krasnegor, National Institutes of Health
Robert C. MacPhail, U.S. Environmental Protection Agency
Suzanne McMaster, U.S. Environmental Protection Agency
Lakshmi C. Mishra, U.S. Consumer Product Safety Commission
Andres Negro-Vilar, National Institute of Environmental Health Sciences
James K. Porter, U.S. Department of Agriculture/Agricultural Research Service
Lawrence W. Reiter, U.S. Environmental Protection Agency
Jane Robens, U.S. Department of Agriculture/Agricultural Research Service
Barry Rosloff, Food and Drug Administration
Harry Salem, U.S. Army Chemical Research, Development, and Engineering Center
Bernard A. Schwetz, National Institute of Environmental Health Sciences
William F. Sette, U.S. Environmental Protection Agency
William Slikker, Jr., National Center for Toxicological Research
D. Stephen Snyder, National Institute on Aging
Thomas J. Sobotka, Food and Drug Administration
Hugh A. Tilson, U.S. Environmental Protection Agency
Mildred Williams-Johnson, Agency for Toxic Substances and Disease Registry

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Part IV

Department of Justice

Immigration and Naturalization Service

8 CFR Parts 242 and 287

**Enhancing the Enforcement Authority of
Immigration Officers; Final Rule**

DEPARTMENT OF JUSTICE

Immigration and Naturalization Service

8 CFR Parts 242 and 287

[INS No. 1442-92; AG ORDER 1907-94]

RIN 1115-AC63

Enhancing the Enforcement Authority of Immigration Officers

AGENCY: Immigration and Naturalization Service, Justice.

ACTION: Final rule.

SUMMARY: This final rule implements changes to Immigration and Naturalization Service (Service) procedures that relate to carrying firearms, expanding the arrest and service of process authority of immigration officers beyond matters involving violations of the immigration laws, and requiring that every alien fourteen years of age or older, against whom deportation proceedings are commenced, shall be fingerprinted and photographed and that such fingerprints and photographs shall be made available to other law enforcement agencies upon request. This rule also codifies existing policy guidelines regarding the authority of immigration officers under the direction and control of the Attorney General to arrest persons, carry firearms, serve process, and perform other related enforcement functions. The final rule affirms both existing and newly-developed policies and ensures the consistent application of these policies by all immigration officers involved in the enforcement of the immigration laws.

EFFECTIVE DATE: August 17, 1995.

FOR FURTHER INFORMATION CONTACT: Kathryn E. Sheehan, Special Assistant, Immigration and Naturalization Service, 425 I Street NW., Room 7246, Washington, DC 20536, telephone (202) 514-3032.

SUPPLEMENTARY INFORMATION: On October 14, 1992, at 57 FR 47011-47020, the Attorney General published a proposed rule to implement section 503 of the Immigration Act of 1990 (IMMACT), Public Law No. 101-649 (8 U.S.C. 1357), and requested comments from interested parties by November 30, 1992. Section 503(a) of IMMACT amended section 287 of the Immigration and Nationality Act (Act). Section 503(a) authorizes immigration officers, when performing duties relating to the enforcement of the immigration laws and when authorized under regulations prescribed by the Attorney General, to arrest without a warrant any person likely to flee before a warrant can be

obtained, for any offense against the United States committed in the officer's presence or for any felony cognizable under the laws of the United States if the officer has reasonable grounds to believe the person to be arrested has committed or is committing such a felony. Section 503(a) of IMMACT also authorizes immigration officers, under regulations prescribed by the Attorney General, to carry firearms and to execute and serve any orders, warrants, subpoenas, summonses, or other process issued under the authority of the United States.

Section 503(b) of IMMACT requires fingerprinting and photographing of any alien fourteen years of age or older against whom deportation proceedings have been commenced under section 242 of the Act, and dictates that such fingerprints be made available to law enforcement agencies upon request. Finally, section 503(a) of IMMACT requires, as a condition of immigration officers' authority to make warrantless arrests under amended section 287(a)(5)(B) for felonies, the Attorney General to publish final regulations that define the categories of immigration officers who may use force, including deadly force, and the circumstances under which such force may be used; establish standards with respect to enforcement activities of the Service; require that no immigration officer be authorized to make arrests under section 287(a)(5)(B) of the Act unless that officer has been certified as having completed a training program covering such arrests and standards and establish an expedited internal review process for violations of such standards.

The proposed rule set forth regulations implementing these provisions of section 503 of IMMACT. A total of 235 comments were received, reviewed, and considered in writing this final rule.

General Issues

Five commenters stated that the proposed rule failed to comply with section 4(b) of E.O. 12291 as it relates to the comments of persons directly affected by the rule, and sections 2(a) and 2(b)(2) of E.O. 12778 as they relate to adherence to certain requirements in promulgating new regulations and reviewing existing regulations.

Many of the provisions of E.O. 12291 pertain only to major rules. In the proposed rule, the Attorney General stated that this rule is not a major rule within the meaning of section 1(b) of E.O. 12291. Therefore, section 4(b) of that Executive Order is inapplicable. With regard to E.O. 12778, the Office of Management and Budget (OMB) issued

a Memorandum for Agency Regulatory Contacts dated January 9, 1992, stating that there are two ways that an agency may certify compliance to OMB as part of the regulatory review process. An agency may attach a certification of compliance with E.O. 12778 to Standard Form 83 signed by an attorney, or an agency may insert a statement of such certification in the preamble to the draft rule itself. The Department of Justice (Department), following review of the rule in light of E.O. 12778 and in compliance with that Executive Order, attached a certification of compliance. Accordingly, the Department and the Service believe that the requirements of E.O. 12291 (which was superseded by E.O. 12866 on September 30, 1993), 12866, and 12778 have been met.

One commenter stated that the proposed rule may be in violation of the Service's contract with its collective bargaining unit because the required negotiations have not occurred regarding those aspects of the rule that constitute substantive changes in conditions of employment affecting the bargaining unit. During development of the final rule, negotiations occurred with both the National Immigration and Naturalization Service Council and the National Border Patrol Council.

One commenter asserted that the existing Service Firearms Policy could not be changed because it constituted an agreement with the employee unions. The Service disagrees because there is no agreement between it and the employee unions regarding the existing Service Firearms Policy.

One commenter pointed out that the proposed rule failed to indicate whether the regulations would preempt state or local laws regarding peace officer status. The regulations implement new statutory authorities pertaining to arrests and service of process for federal matters and would not affect current practices with states. State law may provide immigration officers with peace officer status that would also provide the authority to make arrests for state law violations. However, unless specifically authorized as a peace officer under state law, an immigration officer's authority to enforce the state statute is that of an ordinary citizen. The limitations and liabilities associated with such action are defined in state law.

One commenter stated that the proposed regulations appeared to conflict with sections 101(a)(18) and 235 of the Act as they relate to the definition of "immigration officer" and an immigration officer's authority to administer oaths, take and consider evidence, and require by subpoena the

attendance and testimony of witnesses and production of documents. The Service disagrees. Section 101(a)(18) of the Act authorizes the Attorney General to designate, individually or by regulation, any employee or class of employees to perform the functions of an immigration officer specified by the Act or any section thereof. In the proposed regulations, the Attorney General accomplished this by designating those categories of immigration officers authorized to perform the functions of sections 242 and 287 of the Act. The commenter stated incorrectly that § 287.5(a) of the proposed rule required certain immigration officers to obtain individual or class designation in order to be authorized to interrogate and administer oaths. The proposed rule in § 287.5(a) allowed any immigration officer as defined in 8 CFR 103.1(g) to interrogate and administer oaths. With regard to subpoenas, the proposed rule made no changes to the current regulations in § 287.4 pertaining to the subpoena process.

A number of commenters criticized the proposed rule for not providing a sufficient statement of the legislative history of section 503 of IMMACT in the Summary section. An adequate description of the requirements of section 503 was provided by the notice of proposed rulemaking in the Supplementary Information section of the rule in accordance with the Federal Register's document drafting requirements.

One commenter recommended that the effective date of the final rule for other than permanent full-time (OTP) immigration inspectors be extended to two years from date of publication in the *Federal Register* in order to have sufficient time to provide both basic immigration law enforcement training and training in the new enforcement standards. Such an extension is impracticable as many permanent full-time immigration officers will also need to receive both basic immigration law enforcement training and training in the new enforcement standards. It would be inappropriate to allow the OTP immigration officers to take more time in meeting the training timetable than the permanent full-time employees because this would result in having OTP immigration inspectors operating under the old regulations while working side by side with permanent full-time immigration inspectors recently trained in, and operating under, the new regulations. This situation would not only promote procedural inconsistencies and confusion, but also subject the public to two different

regulatory standards at ports of entry. The Attorney General has delayed implementation of the final rule to one year from date of publication in order to ensure training of approximately 10,000 immigration officers in the new enforcement authorities and standards. The Attorney General recognizes the difficulties inherent in meeting this rigorous training schedule. However, she is committed to ensuring a consistent and unified implementation approach nationwide that only one delayed implementation date can provide.

Policy Issues

Sections 242.2 and 287.7—Apprehension, Custody, and Detention and Retainer Provisions

One commenter stated that the proposed rule was contradictory by requiring that an immigration officer successfully complete basic immigration law enforcement training in order to be authorized to issue a detainer in §§ 242.2(a) and 287.7(a), yet not requiring the successful completion of basic immigration law enforcement training in order to be authorized to issue an order to show cause in § 242.1(a) or a warrant of arrest in § 242.2(c). A detainer is the mechanism by which the Service requests that the detaining agency notify the Service of the date, time, or place of release of an alien who has been arrested or convicted under federal, state, or local law. The Service agrees with the commenter that the standards for issuance of a detainer are no greater than those for issuance of an order to show cause and a warrant of arrest for immigration violations. The final rule deletes the requirement of successful completion of basic immigration law enforcement training for authorization to issue detainers. Training in immigration law and procedure is necessary to issue detainers, but training as a law enforcement officer is not needed to effectively conduct this portion of the immigration process. This does not eliminate the immigration officer's responsibility to ensure that detainees are issued only to aliens who are amenable to exclusion or deportation proceedings.

Two commenters stated that the authority to issue a warrant of arrest in § 242.2(c) should include the authority to serve the warrant of arrest in § 287.5(e)(2). The Service disagrees. Issuance of a warrant of arrest entails signature by an authorized immigration officer, while service of the warrant entails a step-by-step process requiring training and proficiency in service of

process procedures. The two authorities are separate and distinct processes.

Section 287.1—Definitions

One commenter urged the inclusion of the Other Than Permanent Full-Time (OTP) Immigration Inspector Basic Training Course in the definition of "basic immigration law enforcement training" in § 287.1(g). The Service agrees and this section has been amended accordingly. However, an OTP immigration inspector will not be authorized to make arrests for federal offenses under section 287(a)(5) (A) and (B) of the Act until such time as he or she converts status to permanent full-time and successfully completes training applicable to that position.

Four commenters urged the Service to expand the definition of "basic immigration law enforcement training" in § 287.1(g) to include prior law enforcement experience or training with other federal, state, or local agencies as well as lengthy Service experience or other miscellaneous Service training courses apart from the basic training courses. The Service acknowledges that successful completion of one or more training courses presented by the Federal Government or a state-certified program may be substantially equivalent to basic immigration law enforcement training. The final rule provides a mechanism for considering other training by expanding the definition of "basic immigration law enforcement training" to include training that is substantially equivalent thereto as determined by the Commissioner with the approval of the Deputy Attorney General. The Commissioner's review is necessary to ensure that each immigration officer has all the required federal and, in particular, immigration law enforcement training. For example, an immigration officer who was employed previously in another Federal agency as a special agent, and thus had training in general Federal laws, would still need immigration law enforcement training.

Sections 287.5 and 287.9—Exercise of Power by Immigration Officers and Criminal Search Warrant and Firearms Policies

Ninety-eight commenters expressed concern that the proposed regulations precluded immigration officers from carrying firearms in §§ 287.5(f) and 287.9(b), effecting arrests for immigration violations in § 287.5(c) (1), (2), and (5), and serving process in § 287.5(e) while off duty. The commenters stated that it is not uncommon for immigration officers or other federal law enforcement officers in

an off-duty status to receive telephone calls at home from other federal, state, or local law enforcement officers requesting their immediate assistance. The commenters pointed out that only §§ 287(a)(5) (A) and (B) of the Act, regarding arrest authority for federal offenses, stipulate that an immigration officer must be "performing duties relating to the enforcement of the immigration laws at the time of the arrest" and that this language should not be included in those sections of the proposed rule regarding the other enforcement authorities. In drafting the proposed rule, the Service did not intend to impair an immigration officer's ability to place himself or herself on duty when necessary for the purpose of enforcing the immigration laws of the United States. To avoid misinterpretation, the Service has removed the language "performing duties relating to the enforcement of the immigration laws at the time of the arrest" from the enforcement authorities except where required by statute. The Service has also removed the language "In an on duty status" from § 287.9(b). Administrative guidelines will be developed to explain when an immigration officer on his or her own initiative may place himself or herself in an on-duty status.

Fifty-two commenters objected to establishing a separate process for Service managers, including district directors, deputy district directors, officers in charge, and assistant officers in charge, to request the Commissioner's authorization to exercise each of the enforcement authorities. The commenters stated that this process would hold managers to a higher standard than their subordinates, many of whom are trainees still on probation, who are automatically empowered to exercise an authority if they have completed the requisite training. The commenters asserted that this process violates standard management hierarchy, and pointed out that the vast majority of affected individuals are career immigration officers who not only have completed basic immigration law enforcement training, but also have extensive experience in field enforcement operations. In fact, due to the Service's limited enforcement resources, these managers participate frequently in Service field enforcement operations or respond to requests for assistance from other law enforcement agencies when their subordinates are out of the office conducting field operations. The commenters asserted that managers in other agencies within the Department, including the Federal

Bureau of Investigation, are vested with the same powers and authorities as their subordinates, and the Service's managers should not be treated differently if they have undergone the requisite training.

The Service and the Department agree that a more streamlined process should be established for granting enforcement authorities to Service managers who are trained and who have maintained qualifications. The rationale behind the proposed rule's segregation of managers was to ensure that law enforcement authorities are granted only to those immigration officers, regardless of rank, who need the authorities and are fully trained in how to exercise them. To accomplish this task more expediently while ensuring the existence of a well-trained cadre of immigration officers at all levels in the agency, the final rule provides enforcement authorities to managers who have successfully completed basic immigration law enforcement training without creating a separate authorization process. The final rule also provides a mechanism for empowering those managers, as well as other immigration officers within one of the designated categories, who have not successfully completed one of the basic immigration law enforcement training courses by allowing them either to attend one of the basic immigration law enforcement training courses or to seek a determination from the Commissioner, with the Deputy Attorney General's approval, that they have training substantially equivalent thereto.

A number of commenters stated that each immigration officer should have the power to exercise all of the enforcement authorities as long as each such officer is trained and certified. They stated that the proposed regulations created a rigid class system wherein only certain categories of immigration officers would be authorized to exercise certain enforcement functions and that this system impedes the Service's ability to respond to operational emergencies. In addition, some commenters stated that the enforcement role of immigration inspectors at ports of entry and the field review work and office interviews conducted by immigration examiners necessitate empowering both inspectors and examiners with all of the enforcement authorities. The Service and the Department disagree. In drafting the proposed rule, the Service used the Attorney General's "Guidelines for Legislation Involving Federal Criminal Law Enforcement Authority" (Guidelines) dated June 29, 1984. Although the Guidelines were developed to guide federal agencies in

preparing legislative proposals concerning future grants of law enforcement authority, the Guidelines' overriding policy is that an officer should be given only the authorities that the officer needs and has been trained to execute. The Guidelines require an agency to extend grants of law enforcement authority only to those employees who have graduated from an accredited course of training in the exercise of that authority and only where a significant likelihood exists that, in the course of performing their assigned duties, the employees will frequently encounter situations in which it is necessary to exercise that authority. Each category of immigration officers has a different mission, and only those categories who satisfied the Attorney General's criteria were granted one or more of the enforcement authorities. In reviewing these regulations, consistent with the Department's review of other regulations, guidelines, and policies affecting criminal law enforcement authority in the Executive Branch, the Department believes that the same delineation of authorities is both appropriate and effective. The following chart summarizes the categories of immigration officers who are authorized to exercise the principal enforcement authorities.

Some commenters stated that immigration inspectors at ports of entry need the authority to execute arrest warrants for immigration violations to conform with historical practices of the United States Attorneys' offices. In light of existing practices, the Service and the Department agree that immigration inspectors at ports of entry do need to continue executing arrest warrants for both criminal and administrative immigration violations. However, immigration inspectors do not need the authority to execute arrest warrants for non-immigration criminal violations. The investigation of non-immigration criminal offenses associated with the authority to execute an arrest warrant for non-immigration violations is beyond the scope of an immigration inspector's responsibilities. Accordingly, the structure of § 287.5(e) in the final rule has been changed to focus on the distinction between "immigration" and "non-immigration" offenses, and to grant authority to immigration inspectors to execute arrest warrants for immigration violations.

The revised language of § 287.5(e) also specifies, as the structure of the proposed rule specified, that detention enforcement officers are authorized only to execute warrants of arrest for administrative immigration violations,

not warrants for a criminal arrest that can be executed by other officers. In carrying forward this distinction, the Commissioner is authorized to designate additional officers (individually or as a class) to execute warrants of arrest for administrative immigration violations, while approval of the Deputy Attorney General must be sought to designate additional officers (individually or as a class) to execute criminal arrest warrants. Finally, § 287.5(e)(2)(ii) grants authority to execute criminal warrants of arrest for non-immigration violations only to border patrol agents, special agents, deportation officers, their supervisors and managers, and immigration officers who need such authority and who have been designated by the Commissioner with the approval of the Deputy Attorney General.

Several commenters questioned the efficacy of granting immigration examiners the power to arrest for immigration violations in §§ 287.5(c) (1) and (2) yet not authorizing them to carry firearms in § 287.5(f). Similarly, other commenters stated it was inappropriate to authorize detention enforcement officers to carry firearms yet preclude them from effecting any arrests. The Service and the Department disagree. The ability to effect an arrest is not conditioned upon the carrying of a firearm. Other federal, state, and local law enforcement officers' duties require them to make arrests without a firearm, and they do so without incident. Similarly, the potential need and ability to use deadly force to defend an officer does not imply a concomitant need for arrest authority. The two authorities are not necessarily concomitant. Detention enforcement officers do not need arrest authority. Detention enforcement officers' principal duties are to transport and guard detained individuals who have already been placed under arrest. They also execute warrants of arrest for administrative immigration violations. In order to clarify the detention enforcement officers' authorities, § 287.59(c)(6) has been added to the final rule.

Five commenters questioned whether immigration examiners and deportation officers who perform inspectional duties at ports of entry on an overtime basis would be precluded from exercising the enforcement authorities granted to immigration inspectors. Immigration examiners, including free trade examiners, and deportation officers are considered to be immigration inspectors when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections, provided all training requirements for

immigration inspectors have been met. To avoid misinterpretation, the Service has added language to the rule stipulating that immigration examiners are authorized to exercise the same enforcement authorities granted to immigration inspectors when they are in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections. Deportation officers are already listed as authorized to exercise the same enforcement authorities granted to immigration inspectors, but § 287.5(b) has been amended for clarification to include deportation officers only when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections.

Two commenters stated that certain immigration officers stationed in Service offices overseas should be granted law enforcement authority. They also noted that immigration officers stationed overseas occasionally must work on cases within the United States. The Service and the Department note, however, that immigration officers cannot exercise any of the enforcement authorities while working in foreign countries. When overseas officers are assigned to a duty post within the United States, they assume the power to exercise all of the criminal and civil enforcement authorities assigned to the applicable category of immigration officers, provided all training requirements have been met. For example, a special agent overseas who is detailed to an assignment in the United States has all of the enforcement authorities granted to special agents, provided that the detailed special agent has met all training requirements for special agents. However, overseas immigration officers do need the authority to interrogate, administer oaths, and take and consider evidence. Accordingly, § 287.5(a) in the final rule has been amended to grant such officers authority to interrogate, administer oaths, and take and consider evidence in or outside the United States.

One commenter stated that the proposed rule in § 287.8(c)(2) should be changed to remove the requirement that the immigration officer must document, on appropriate Service forms, the fact that an arrestee was advised of his or her rights. The commenter pointed out that many United States Attorneys accept advice of rights given in the presence of witnesses in lieu of a form. The Service disagrees. Immigration officers must document advice of rights on appropriate Service forms, consistent

with the practice of other components within the Department.

One commenter suggested that proposed § 287.8(c)(2) incorrectly stated that a person arrested and charged with a criminal violation shall be advised of the appropriate rights as required by law at the time of arrest, or as soon thereafter as practicable. The commenter pointed out that current law requires that such warnings be provided only prior to a custodial interrogation. The commenter further stated that many criminal arrests are made where the arresting officer does not want to conduct a custodial interrogation and therefore should not be required to advise the person arrested of the appropriate rights. The Service and the Department disagree with the commenter's interpretation of the rule. First, the rule states that the person arrested shall be advised of the appropriate rights as required by law. The law, including constitutional standards, determines when advice of rights must be provided. Second, to the extent that the rule encourages a uniform advice of rights at or shortly after the point of arrest, it serves as an appropriate reminder of these constitutional standards and establishes a practice that will prevent situations where interrogations are wrongfully undertaken without proper advice of rights.

One commenter stated that the definition of a designated pursuit vehicle in § 287.8(e)(1) should stipulate that the vehicle must be a sedan in order to conform to the Border Patrol Vehicle Pursuit Policy. The Service disagrees. Other enforcement programs will be developing their own vehicle pursuit policies that may permit the use of vehicles other than sedans. The proposed regulations authorized certain categories of immigration officers, including special agents and deportation officers, to initiate a vehicular pursuit. In the final rule, special agents and deportation officers have been removed from the list until such time as the Investigations and the Detention and Deportation Programs have developed their specific vehicle pursuit policy, the policy is approved by the Commissioner, and all of the special agents and/or deportation officers authorized to initiate vehicular pursuits have undergone the requisite pursuit driving training and received training in the new policy.

Section 287.10—Expedited Internal Review Process

One commenter questioned the legitimacy of the Service's Office of Internal Audit, stating that the Service

is trying to create by regulation an office similar in function to the Office of Professional Responsibility, which was transferred from the Service to the Office of the Inspector General of the Department pursuant to section 102(d) of the Inspector General Act Amendments of 1988, Pub. L. No. 100-504. The Service and the Department disagree. The Office of Internal Audit was established in the reorganization of the Service and approved by the Attorney General in April 1991. Regulations have been drafted wherein the Director of Internal Audit is responsible, in part, for providing the capability to investigate alleged misconduct by Service employees and for coordinating that program with other agencies within the Department. The transfer of the Office of Professional Responsibility from the Service to the Office of the Inspector General neither relieved Service management from responsibility for ensuring proper employee conduct nor precluded Service management from exercising its fundamental management authorities to identify and correct employee misconduct.

One commenter stated that the proposed rule in § 287.10 was insufficiently specific because it stated only that allegations of misconduct would be referred "promptly" and did not: describe how the process for resolution would be expedited; describe the circumstances under which a Service employee, against whom allegations were made, might not be notified of the allegations; indicate that more serious allegations would be handled differently than less serious ones; call for the involvement of operational peers or supervisors in resolving allegations; and eliminate from involvement in the process management officials who lack law enforcement experience. It is not appropriate to incorporate the specific requirements for the handling of alleged violations of the enforcement standards into administrative rulemaking, and therefore, no change has been made to the final rule.

Legal Sufficiency

Sixty-nine advocacy organizations and individuals filed substantially similar or identical comments stating that the regulations are legally insufficient to meet the legislative mandate set forth by Congress. These comments are generally summarized below and followed by specific comments and responses.

The commenters stated that the regulations are legally insufficient because they fail to comply with the

congressional mandates: (1) to define the enforcement authority; (2) to elaborate on the scope and limits of such authority and to formulate written policies, directives, rules, and regulations to ensure the exercise of that authority within those limits; (3) to provide training for officers in how to exercise the discretionary authority granted; and (4) to outline a formal procedure for agency accountability to the community when the authority has been exercised. The commenters stated that the regulations are insufficiently specific and detailed on each of these subjects.

While the Service agrees with many of the suggestions regarding appropriate law enforcement standards as consistent with Department policy applicable to all law enforcement agencies, the Service disagrees that these regulations are either the appropriate vehicle to specify the detail of such standards, or that Congress mandated such a degree of specificity. The commenters effectively requested that the Service and the Department provide specific guidelines for discretionary decisions under other legal constraints and sound judgment, detailed procedures of daily operation, and substantive training materials, timetables, and protocols that are encompassed in enforcement manuals, supervisory review procedures, and training curricula. For reasons discussed in greater detail below, the Service will not provide this information and guidance in regulatory form; the Department declines to make an exception to standing policies for the management of the criminal justice system in the Executive Branch.

The suggestions made by these comments are appropriately directed to the functions of training and management, not administrative rulemaking. The Service and the Department agree with many of these suggestions, and, as noted below, have either incorporated them into existing training and management guidelines or are in the process of doing so. A section-by-section discussion of these comments follows.

Section 287.1(g)—Training

The commenters criticized § 287.1(g) for not providing sufficient detail regarding the substance of the training that must be completed by Service officers prior to assuming the new enforcement authority provided by section 503 of IMMACT. The commenters noted that neither the course subjects, length, nor materials are specified, and stated that the regulations should at the very least indicate how the

curriculum of existing Service training programs will be amended.

The commenters also alleged that "nothing new" is added by these regulations because all Service officers have already completed one course of basic immigration law training. The commenters suggested that the regulations should require that Service officers attend additional training before assuming additional enforcement authority. Finally, the commenters suggested that the regulations should require periodic attendance by Service officers at national or local training events devoted to new legal standards, case decisions, and Service interpretations of the law.

In response, the Service notes that these commenters appear to have assumed that Service officers who have previously completed a course of basic immigration law enforcement training will not be required to undergo additional training before being authorized to undertake the enhanced enforcement authority prescribed in section 503. However, § 287.5(c)(4)(iii) of the proposed rule specifically stated that no immigration officer could assume enhanced arrest authority until the Director of Training had certified that the immigration officer had completed a training course encompassing such arrests and the standards for enforcement activities specified in § 287.8 of the regulations. Virtually all affected officers will receive additional training during the planned one-year interval between the publication in the *Federal Register* of this final rule and its effective date. This training is currently being developed in conjunction with other components of the Department to ensure that the training is consistent with existing training on the execution of law enforcement authorities and the investigative and prosecutorial policies of the Department.

The Service agrees that existing training courses in basic law enforcement should be amended to include the training required by section 503; these curricula are in the process of being revised. Furthermore, the Service agrees that officers should receive training throughout their careers regarding new statutes, legal precedent, and policies for enforcement. Service guidelines and training programs will be continually updated to meet these needs. Precisely because judicial precedent and the Department's investigative and prosecutorial policies are constantly evolving, the Department concludes that it is not appropriate to further specify in regulations the curricula or frequency of training

programs. Moreover, daily supervision to ensure compliance with legal standards enunciated by Congress and the courts is generally more effective and efficient than developing detailed statements in the form of regulations that cannot provide guidance in all situations.

Sections 287.5(a)(1) and 287.8(b)—Power to Interrogate and Detain

The commenters suggested that the concept of a "show of authority" to restrain the freedom of an individual to walk away under § 287.8(b)(1) be expanded to specifically include verbal or psychological abuse. The term "show of authority" in the proposed rule was intended to emphasize the intimidating gestures are prohibited during pre-detention questioning. However, the Service has decided to eliminate the term "show of authority" as well as the language "by means of physical force" in the final rule, thereby clarifying that any action taken by an immigration officer during pre-detention questioning must not lead the person being questioned to believe that he or she is not free to leave the presence of the officer. The Service's training program will ensure that all immigration officers have a thorough understanding of proper procedures for conducting pre-detention questioning.

The commenters also suggested that § 287.8(b)(2) be substantially amended to include current judicial precedent defining "reasonable suspicion" and the general authority to interrogate and detain. Binding judicial precedent such as *Brewer v. Williams*, 430 U.S. 387 (1977), is subject to revision in the ongoing process of litigation, and would not be appropriate to codify.

Sections 287.5(c) and 287.8(c)—Power and Authority to Arrest

The commenters generally stated that the provisions in §§ 287.5(c) and 287.8(c) do not incorporate the "standard with respect to enforcement" mandated by section 503 of IMMACT. The commenters suggested that the regulations be amended to incorporate the judicial construction of "reason to believe," and to require compliance with outstanding court orders regarding arrest and post-arrest procedures. As stated previously, judicial precedent and other policy standards are subject to revision and are not appropriate to codify. The Service is clearly bound by such interpretations, including those set forth in *Gerstein v. Pugh*, 420 U.S. 103 (1975). Furthermore, the Service is bound to comply with outstanding court orders, and a regulatory provision to that effect is unnecessary. The

commenters also suggested that the specific provisions of a temporary settlement agreement in *Lopez v. INS*, No. CV 78-1912-WMB (C.D. Cal. August 24, 1992), be incorporated into the final rule. The Service declines this suggestion for the previously stated reasons, as well as for the fact that nothing in the *Lopez* case has required the Service to promulgate regulations on this subject.

One commenter criticized these sections for permitting individuals who have not fulfilled the statutory training requirement for enhanced arrest authority to be designated as service officers with arrest authority. However, all officers who are designated to have such authority must receive the appropriate training pursuant to §§ 287.5(c)(4) (iii)-(iv). The commenter also stated that § 287.5(c)(5), in specifying the authority for arrests under section 274 of the Act, failed to distinguish adequately between arrests with and without a warrant. However, this section of the rule incorporates the enforcement standard regarding arrests set forth in § 287.8(c), which includes a rule requiring officers whenever possible to obtain a warrant prior to arrest. In criminal cases, pursuant to § 287.5(c) (2) and (3), the issuance of such a warrant is reviewed by an Assistant United States Attorney and a Magistrate Judge before an arrest is effected.

Sections 242.2(c)(1) and 287.5(e)(2)—Arrest Warrants

The commenters stated that § 242.2(c)(1) should be amended to provide that an arrest warrant must be obtained unless there is a likelihood of the alien escaping before a warrant can be obtained. This suggestion calls for codification of the judicial precedents concerning exigent circumstances. For the reasons stated previously, the Department does not deem it appropriate to amend this rule to reflect evolving judicial standards. Such standards are incorporated into Service training programs, enforcement guidelines, and manuals.

The commenters also suggested that the rule should specify which factors Service officers should use to determine the likelihood of escape. This is the type of discretionary detail that is appropriate in a training course and manual, but not in a regulation. Finally, the commenters suggested that evidence obtained in violation of rules requiring warrants should be suppressed in civil deportation hearings. The Department declines to extend by regulation into civil proceedings the exclusionary rule,

which has heretofore been applied exclusively in criminal proceedings.

Sections 287.5(d)-(e) and 287.9(a)—Searches

The commenters stated that the rule should provide specific standards governing searches of persons and property at or inside the border; strip and body cavity searches; vehicle stops and searches of persons and vehicles at or inside the border; and searches of private dwellings and lands. Section 503 of IMMACT does not require such specificity in enforcement regulations. Moreover, for that reasons set forth above, such standards will be appropriately addressed in Service training programs, guidelines, and enforcement manuals.

Sections 242.2(a)(1) and 287.7(a)(1)—Detainers

The commenters stated that the authority for issuance of detainers in §§ 242.2(a)(1) and 287.7(a)(1) of the proposed rule was overly broad because the authority to issue detainers is limited by section 287(d) of the Act to persons arrested for controlled substances offenses. This comment overlooked the general authority of the Service to detain any individual subject to exclusion or deportation proceedings. See 8 U.S.C. 1225(b), 1252(a)(1). The detainer authority of these sections of the proposed rule were promulgated pursuant to this general authority. The statutory provision cited by the commenters places special requirements on the Service regarding the detention of individuals arrested for controlled substance offenses, but does not delimit the general detainer authority of the Service.

Section 287.8(d)—Vehicle Transportation

The commenters suggested that the Service install seat belts in all vehicles transporting people. Current regulations under which all motor vehicles, except buses, are manufactured require the factory installation of seat belts. While the Service strongly agrees with the substance of the suggestion, it would be inappropriate to include any additional requirements within an administrative rule. The reference to seat belts has been deleted in the final rule because the standard governing the use of seat belts will be thoroughly addressed in Service training programs, guidelines, and enforcement manuals.

Section 287.8(e)—Vehicular Pursuits

The commenters stated that the provisions of this section provided inadequate protection to public safety

from accidental injury and death resulting from collisions following high-speed vehicular pursuits. The commenters suggested that the rule provide that a vehicular pursuit may not be initiated "when there is imminent danger to the life and safety of innocent third parties." In response to a number of publicized incidents, the Service revised its guidelines and procedures governing vehicular pursuits. However, it would be inappropriate for the Department to codify the standard suggested by these commenters in the final rule. The standard is both unduly restrictive and underinclusive. Actual operating standards for Service officers must permit greater discretion and also specify in greater detail the criteria that should be considered in deciding whether to undertake a pursuit.

The commenter also suggested that officers should be required to successfully complete a separate course in vehicle pursuit prior to having authority under this section. The Department agrees that only those officers specifically trained in pursuit techniques should be authorized to undertake a vehicular pursuit. The only such officers at present who have received such training are border patrol agents. Accordingly, this section has been amended to delete the designations of special agents and deportation officers.

Section 287.8(f)—Site Inspections

The commenters stated that this section was legally insufficient and should provide more detailed requirements concerning the obtaining of warrants and consent for site inspections, the determination of "exigent circumstances," and standards and procedures for detention. Commenters specifically suggested that the rule incorporate judicial precedent based on the Fourth Amendment to the Constitution concerning the issuance of warrants, the obtaining of consent to enter a premises, and the detention of persons subject to questioning; that officers engaged in site inspections be trained in standards of enforcement and procedure pertaining to site inspections; that Service officers not deliberately provoke flight by persons in order to justify entry onto a premises; and that Service officers avoid "unnecessary embarrassment" of persons subject to site inspections, as well as verbal abuse, psychological abuse, threats, and unnecessary physical force.

The Service agrees with the substance of most of the suggestions made by the commenters, but has not incorporated these suggestions into the final rule. For the reasons stated previously, the

Department does not consider it appropriate to incorporate evolving judicial precedent into regulations. Such precedents are included in Service training programs, guidelines, and enforcement manuals. In addition, many of the procedural suggestions made by these commenters either are included in current Service training programs, guidelines, and enforcement manuals or will be considered for inclusion in these materials.

The Department has also revised the ordering of the paragraphs within this section and has revised the text of paragraph (2) in the proposed rule, now designated as paragraph (4). The purpose of these changes is to clarify that the conditions set forth in this section for the conduct of site inspections do not restrict the authority of Service officers to enter into any area of a business or other activity to which the general public has access or onto open fields that are not farm or other outdoor agricultural operations without a warrant, consent, or any particularized suspicion.

Sections 287.5(f), 298.8(a) and 287.9—Use of Force and Firearms

The commenters criticized these provisions of the proposed rule on a number of grounds. The commenters stated that the rule failed to address the 27 recommendations presented in the Audit Report, "Immigration and Naturalization Service Firearms Policy, September 1991," prepared by the Department's Office of the Inspector General, Audit Division. The commenters asserted that the rule's statement that standards on the use of force are based on a force continuum model taught at the Federal Law Enforcement Training Center is inadequate and that the rule should adopt the recommendations of standards for law enforcement agencies developed by the Commission on Accreditation of Law Enforcement Agencies. The commenters also stated that the rule was too narrow in its statement of the authority to carry firearms; the commenters recommended that the rule adopt guidelines that reflect the "multiple psychological dimensions" that might influence an officer's behavior. The commenters also urged that the rule incorporate a statement of 15 Shooting Reduction Techniques published in 1985 by the American Bar Foundation. The commenters stated that the principle of proportionality must be specifically set forth in the rule's guidelines on the use of force along with more specific guidelines on the use of force in specific

situations that immigration officers are likely to encounter.

The Service agrees that many of the recommendations made by the commenters are sound and should be incorporated into the training of immigration officers. In fact, a significant portion of the Service firearms training program is devoted to judgment shooting that includes providing specific scenarios that immigration officers are likely to face. However, as a matter of Departmental policy, it is not appropriate to incorporate such detailed guidelines for law enforcement activities into administrative rulemaking. Most of the recommendations made by the Inspector General in the Audit Report have been, or are in the process of being, adopted or implemented by the Service. The commenters noted that, in a letter dated August 7, 1991, the Commissioner stated that the issues raised by the Audit Report would be addressed in the process of drafting these regulations. The recommendations of the Audit Report have been taken into account in the formulation of this rule. Given the increased training that has been and is being developed, no specific response to these recommendations is provided in the regulatory text.

Several of the commenters criticized the designation of certain Service officers to carry firearms. The Service disagrees with the suggestion that there is no justification for immigration inspectors or deportation officers to carry firearms; this authority is consistent with Department policy in the implementation of other criminal law enforcement authorities. Such authority is commensurate with the responsibility of such officers to exercise general arrest and control authority at frequent points of contact with potential criminal offenders. These officers have also been authorized to carry firearms for many years. The same commenters criticized the rule's delegation to the Commissioner of authority to designate certain other immigration officers to carry firearms, and stated that any such designations must be the subject of proposed rulemaking in accordance with the Administrative Procedure Act (APA). Neither section 503 of IMMACT nor the APA requires such discretionary grants of law enforcement authority, made within general guidelines set forth in regulations, to be the subject of rulemaking. Withdrawing the authority to make such designations would constitute an unwarranted burden on effective law enforcement. Moreover, the Commissioner's action is subject to approval by the Deputy Attorney

General because the authority to carry a firearm is a traditional criminal law enforcement authority, not an authority intrinsic to the Service.

The commenters also criticized § 287.9(b) for failing to specify procedures to be followed in the investigation of a shooting incident involving a Service officer and for failing to provide specific rules regarding loss or theft of an approved firearm, inventory controls on firearms and ammunition, and care and storage of firearms and ammunition. Section 287.9(b) of the proposed rule stated that these matters would be addressed in guidelines promulgated by the Commissioner. It is the view of the Department that since all of these matters relate to internal administration, review, and discipline, the level of detail suggested by the commenters is not appropriate for administrative rulemaking, but should be addressed through operational guidelines. The requirement that these matters be governed according to guidelines promulgated by the Commissioner satisfies the congressional mandate set forth in section 503 of IMMACT.

The commenters also criticized the authorization in § 287.9(b) for Service officers to carry personally owned firearms while on duty, claiming that this will blur the distinction between official and personal use of firearms and inhibit Service control over the use of firearms. The proposed rule required that all firearms, including those personally owned, be approved subject to guidelines to be promulgated by the Commissioner. The authority to utilize a Service-approved, personally owned weapon is needed to respond to the physical diversity of the Service law enforcement workforce, including specific individual characteristics such as the size of an agent's hand. For example, many firearms do not comfortably fit in some smaller or larger hands. Accordingly, the rule is designed to allow flexibility while assuring that each individual agent's firearm has been approved. This is consistent with Departmental policy for the law enforcement community.

Section 287.8(a)(1)—Non-Deadly Force

Several commenters criticized the rule for providing insufficient guidelines on the use of non-deadly force and insufficient inducements for the use of control devices, such as stun guns and gas guns, that do not inflict bodily injury. The commenters also stated that the rule should provide specific requirements for the use of self-defense equipment, including bullet-proof vests and helmets, by Service

officers. The Service issues batons, tear gas, bullet proof vests, and helmets to law enforcement agents, as appropriate, and as appropriated funds permit; the Service does not issue stun guns, gas guns, or other such devices for routine law enforcement purposes. The Service and the Department agree that immigration officers should be trained in a broad range of options in the use of force in order to handle varying situations, that the use of lethal force should be minimized, and that Service officers should be minimized, and that Service officers should be furnished with self-protection equipment and techniques. Such standards cannot be appropriately addressed in rulemaking because of the numerous contingencies that are involved. Service officers are trained in such matters and receive updates in their training to incorporate new law enforcement techniques and new protective devices.

Section 287.8(a)(2)—Deadly Force

The commenters stated that deadly force is an extreme measure and should only be used when an officer reasonably believes it is necessary in defense of human life, including the life of the officer or any person in immediate threat of serious physical harm. To this end, the commenters stated that the rule should require specialized training in specific types of situations to offer guidance to the officer in order to minimize the use of deadly force. Training should include ethics, human rights, and alternatives to the use of force and firearms. "Reasonable belief" and "serious bodily injury" should be defined, according to the commenters, by current judicial standards. The commenters stated that the rule should require that where use of deadly force is likely, the officer should give a warning and allow sufficient time for the warning to be obeyed, but only when the officer or other persons are not at risk.

The Department agrees with many of these suggestions. Furthermore, the rule is consistent with the Department's interpretation of *Tennessee versus Garner*, 471 U.S. 1 (1985), and its progeny, as applied to the missions of the respective Service officers. However, the Department disagrees that these issues can be appropriately addressed in this rule. As stated previously, Service training standards on the use of force are in accordance with prevailing guidelines for all federal law enforcement officials. These guidelines include provisions addressing the issues identified by the commenters.

Section 287.10—Expedited Internal Review Process

The commenters criticized the expedited internal review process proposed in § 287.10 as legally insufficient on a number of grounds. The commenters criticized the proposed rule for incorporating current policies and procedures of the Department's Office of the Inspector General and the Office of Professional Responsibility, stating that these policies and procedures do not provide safeguards that are "accessible and thorough." The commenters stated that the proposed rule provided inadequate notice to the public of its right to lodge complaints. The commenters suggested that an outreach system, including posters, private telephone for detainees, and a 24-hour toll-free number staffed by multi-lingual personnel be mandated in the final rule.

The commenters also stated that a formal procedure for notifying complainants of the receipt and disposition of their complaints should be implemented by the rule. Confidentiality of complaints should be ensured to protect against retaliation, and information obtained in the process of investigation complaints should be excluded from use against the complainant in deportation or exclusion proceedings. The commenters stated that an official record of all complaints, even unsubstantiated complaints, should be retained so that individual officers can be properly evaluated and, if necessary, retrained, counseled, or investigated. Some of the commenters suggested that this information, including unsubstantiated complaints, should be kept in the officer's official personnel file.

The commenters suggested that specific procedures for the investigation of complaints, including provisions for public hearings in the case of serious charges, should be included in the rule. The commenters also stated that an appeals process should be available in cases where complainants or Service officers are dissatisfied with an investigator's report and recommendations. Several commenters also stated that the process for reviewing complaints against Service officers must be improved in order to address allegations of human rights abuses by Service officers patrolling border areas adjacent to Mexico.

In response, the Department notes that many of the suggestions made by these commenters are good practices that are addressed in the policies and procedures of the Department's investigative organizations. However,

many of the specific recommendations regarding notification and timeliness in the completion of investigations are beyond the scope of this rule and must be addressed in these internal policies and procedures. The Department disagrees with the suggestion that an appeals process be provided. Sufficient review of investigatory reports is already provided in the policies and procedures mentioned above. Under these policies and procedures, confidentiality will be maintained in the course of these investigations. If cause for administrative action is found, the administrative process will be followed, and if grounds for civil or criminal prosecution are found, the appropriate litigation will be undertaken. The Department's investigative organizations currently have established procedures to protect the identities of complainants and witnesses from disclosure to Service personnel. Records of unsubstantiated allegations will be centrally maintained by the Service for the purposes identified in the comments and to provide a basis for management review of the number of allegations that have been made to determine whether additional action should be taken at a management level to improve operations and training, but these records will not be kept in an officer's official personnel file.

The commenters also stated that implementation of this section of the rule should be immediate because the reasons for allowing a one-year delay in the provisions of the rule governing enforcement authority do not apply to internal review. The Service and the Department would be in a position to agree if, immediately upon publication of the final rule, the standards were developed and the commensurate training was provided to designated immigration officers. However, the purpose of the one-year delayed implementation period is to enable the Service to develop the standards, provide the training, and certify all designated immigration officers. Because § 287.10 creates an expedited review process exclusively for violations of the standards that will be developed during the one-year implementation period, the effective date of § 287.10 must coincide with all other sections of the final rule. However, this does not alter the established internal review process for alleged violations of existing enforcement policies and procedures.

The commenters also expressed concern that § 287.10(e) of the proposed rule, which would permit Department components to supplement or expand policies and procedures to ensure

proper conduct of Service employees and officers, should not limit or undermine the regulations that govern the review of allegations of improper conduct by Service employees and officers. Neither the Department nor the Service intended that § 287.10(e) be so construed. It is the intention of the Department to provide greater assurances that its officers and employees will conduct themselves appropriately, not to diminish existing standards.

Section 287.11—Disclaimer

The commenters claimed that § 287.11 would preclude victims of unlawful Service enforcement practices from pursuing remedies for regulatory violations. However, this disclaimer merely states that the regulations provide no independent grounds for relief in any civil or criminal proceeding by any party. It does not prevent any party from pursuing relief for alleged violations of the Constitution or laws of the United States. As such, the disclaimer is consistent with the holding in *United States v. Caceres*, 440 U.S. 741 (1979). This disclaimer is a standard element for all regulations affecting substantive federal criminal law enforcement authority and is only intended to ensure that the regulations do not create rights not otherwise existing in law.

Regulatory Flexibility Act

The Attorney General, in accordance with the Regulatory Flexibility Act (5 U.S.C. 605(b)), has reviewed this final rule and, by approving it, certifies that the rule will not have a significant economic impact on a substantial number of small entities.

Executive Order No. 12866

This rule is not considered by the Department of Justice or the Immigration and Naturalization Service to be a "significant regulatory action" under E.O. 12866, section 3(f), Regulatory Planning and Review, and the Office of Management and Budget has waived its review process under section 6(a)(3)(A).

Executive Order No. 12612

The regulations adopted herein will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with E.O. 12612, it is determined that this rule does not have sufficient federalism implications to

warrant the preparation of a Federalism Assessment.

Executive Order No. 12606

The Attorney General certifies that she has assessed this rule in light of the criteria in E.O. 12606 and has determined that this rule will not have an impact on family formation, maintenance, or general well-being.

List of Subjects

8 CFR Part 242

Administrative practice and procedure, Aliens.

8 CFR Part 287

Immigration, Law enforcement officers.

Accordingly, chapter I of title 8 of the Code of Federal Regulations is amended as follows:

PART 242—PROCEEDINGS TO DETERMINE DEPORTABILITY OF ALIENS IN THE UNITED STATES: APPREHENSION, CUSTODY, HEARING, AND APPEAL

1. The authority citation for part 242 continues to read as follows:

Authority: 8 U.S.C. 1103, 1182, 1186a, 1251, 1252, 1252 note, 1252b, 1254, 1362; 8 CFR part 2.

2. Section 242.1 is amended by revising paragraph (a) to read as follows:

§ 242.1 Order to show cause and notice of hearing.

(a) **Commencement.** Every proceeding to determine the deportability of an alien in the United States, except an alien who has been admitted to the United States under the provisions of section 217 of the Act and part 217 of this chapter other than such an alien who has applied for asylum in the United States, is commenced by the filing of an order to show cause with the Office of the Immigration Judge. In the proceeding, the alien shall be known as the respondent. An order to show cause may only be issued by the following immigration officers:

- (1) District directors (except foreign);
- (2) Deputy district directors (except foreign);
- (3) Assistant district directors for investigations;
- (4) Deputy assistant district directors for investigations;
- (5) Assistant district directors for deportation;
- (6) Deputy assistant district directors for deportation;
- (7) Assistant district directors for examinations;
- (8) Deputy assistant district directors for examinations;

- (9) Officers in charge (except foreign);
- (10) Assistant officers in charge (except foreign);
- (11) Chief patrol agents;
- (12) Deputy chief patrol agents;
- (13) Associate chief patrol agents;
- (14) Assistant chief patrol agents;
- (15) The Assistant Commissioner, Investigations;
- (16) Service center directors;
- (17) The Director, Organized Crime Drug Enforcement Task Force (OCDETF);
- (18) Assistant Director, OCDETF (New York, NY; Houston, TX; Los Angeles, CA; and Miami, FL);
- (19) The Assistant Commissioner, Refugees, Asylum and Parole; or
- (20) Supervisory asylum officers.

3. Section 242.2 is amended by revising paragraphs (a)(1) and (c)(1) to read as follows:

§ 242.2 Apprehension, custody, and detention.

(a) *Detainers in general.* (1) A detainer may be issued only in the case of an alien who there is reason to believe is amenable to exclusion or deportation proceedings under any provision of law. The following immigration officers are hereby authorized to issue detainers:

- (i) Border patrol agents, including aircraft pilots;
- (ii) Special agents;
- (iii) Deportation officers;
- (iv) Immigration inspectors;
- (v) Immigration examiners;
- (vi) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(vii) Immigration officers who need the authority to issue detainers in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner.

(c) *Warrant of arrest.* (1) At the time of issuance of the Order to Show Cause, or at any time thereafter and up to the time the respondent becomes the subject of a duly issued warrant of deportation, the respondent may be arrested and taken into custody under the authority of a warrant of arrest. In the case of a respondent convicted on or after November 18, 1988, of an aggravated felony as defined in section 101(a)(43) of the Act, the respondent shall not be released from custody, either before or after a determination of deportability, unless the respondent has been lawfully admitted and the respondent demonstrates to the satisfaction of the district director that he or she is not a threat to the community and is likely to

appear before any scheduled hearings. A warrant of arrest may be served only by those immigration officers listed in § 287.5(e)(2) of this chapter. A warrant of arrest may be issued only by the following immigration officers:

- (i) District directors (except foreign);
- (ii) Deputy district directors (except foreign);
- (iii) Assistant district directors for investigations;
- (iv) Deputy assistant district directors for investigations;
- (v) Assistant district directors for deportation;
- (vi) Deputy assistant district directors for deportation;
- (vii) Assistant district directors for examinations;
- (viii) Deputy assistant district directors for examinations;
- (ix) Officers in charge (except foreign);
- (x) Assistant officers in charge (except foreign);
- (xi) Chief patrol agents;
- (xii) Deputy chief patrol agents;
- (xiii) Associate chief patrol agents;
- (xiv) Assistant chief patrol agents;
- (xv) The Assistant Commissioner, Investigations;
- (xvi) The Director, Organized Crime Drug Enforcement Task Force (OCDETF); or
- (xvii) Assistant Director, OCDETF (New York, NY; Houston, TX; Los Angeles, CA; and Miami, FL).

4. Section 242.4 is revised to read as follows:

§ 242.4 Fingerprints and photographs.

Every alien 14 years of age or older against whom proceedings are commenced under this part by service of an order to show cause shall be fingerprinted and photographed. Such fingerprints and photographs shall be made available to Federal, State, and local law enforcement agencies upon request to the district director or chief patrol agent having jurisdiction over the alien's record. Any such alien, regardless of his or her age, shall be photographed and/or fingerprinted if required by any immigration officer authorized to issue an order to show cause as listed in § 242.1(a).

PART 287—FIELD OFFICERS; POWERS AND DUTIES

5. The authority citation for part 287 continues to read as follows:

Authority: 8 U.S.C. 1103, 1182, 1225, 1226, 1251, 1252, 1357; 8 CFR part 2.

6. Section 287.1 is amended by:

- a. Removing paragraphs (c), (d), and (e);

b. Redesignating paragraphs (f) through (i) as paragraphs (c) through (f) respectively; and

c. Adding a new paragraph (g) to read as follows:

§ 287.1 Definitions.

(g) *Basic immigration law enforcement training.* The phrase *basic immigration law enforcement training*, as used in §§ 287.5 and 287.8 of this part, means the successful completion of one of the following courses of training provided at the Immigration Officer Academy or Border Patrol Academy: Immigration Officer Basic Training Course after 1971; Border Patrol Basic Training Course after 1950; and Immigration Detention Enforcement Officer Basic Training Course after 1977; or training substantially equivalent thereto as determined by the Commissioner with the approval of the Deputy Attorney General. The phrase *basic immigration law enforcement training* also means the successful completion of the Other than Permanent Full-Time (OTP) Immigration Inspector Basic Training Course after 1991 in the case of individuals who are OTP immigration inspectors. Conversion by OTP immigration to any other status requires training applicable to that position.

7. Section 287.2 is revised to read as follows:

§ 287.2 Disposition of criminal cases.

Whenever a district director or chief patrol agent has reason to believe that there has been a violation punishable under any criminal provision of the laws administered or enforced by the Service, he or she shall immediately initiate an investigation to determine all the pertinent facts and circumstances and shall take such further action as he or she deems necessary. In no case shall this investigation prejudice the right of an arrested person to be taken without unnecessary delay before a United States magistrate judge, a United States district judge, or, if necessary, a judicial officer empowered in accordance with 18 U.S.C. 3041 to commit persons charged with offenses against the laws of the United States.

8. Section 287.5 is revised to read as follows:

§ 287.5 Exercise of power by immigration officers.

(a) *Power and authority to interrogate and administer oaths.* Any immigration officer as defined in § 103.1(q) of this chapter is hereby authorized and designated to exercise anywhere in or outside the United States the power conferred by:

(1) Section 287(a)(1) of the Act to interrogate, without warrant, any alien or person believed to be an alien concerning his or her right to be, or to remain, in the United States, and

(2) Section 287(b) of the Act to administer oaths and to take and consider evidence concerning the privilege of any person to enter, reenter, pass through, or reside in the United States; or concerning any matter which is material or relevant to the enforcement of the Act and the administration of the Immigration and Naturalization Service.

(b) *Power and authority to patrol the border.* (1) Section 287(a)(3) of the Act authorizes designated immigration officers, as listed in paragraph (b)(2) of this section, to board and search for aliens, without warrant, any vessel within the territorial waters of the United States and any railway car, aircraft, conveyance, or vehicle within a reasonable distance from any external boundary of the United States; and within a distance of twenty-five miles from any such external boundary to have access, without warrant, to private lands, but not dwellings, for the purpose of patrolling the border to prevent the illegal entry of aliens into the United States.

(2) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the power to patrol the border conferred by section 287(a)(3) of the Act:

- (i) Border patrol agents, including aircraft pilots;
- (ii) Special agents;
- (iii) Immigration inspectors (seaport operations only);
- (iv) Immigration examiners and deportation officers when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections (seaport operations only);
- (v) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(vi) Immigration officers who need the authority to patrol the border under section 287(a)(3) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner.

(c) *Power and authority to arrest.* (1) *Arrests of aliens under section 287(a)(2) of the Act for immigration violations.*

(i) Section 287(a)(2) of the Act authorizes designated immigration officers, as listed in paragraph (c)(1)(ii)

of this section, to arrest any alien, without warrant, who in the presence or view of the immigration officer is entering or attempting to enter the United States in violation of any law or regulation made in pursuance of law regulating the admission, exclusion, or expulsion of aliens, or to arrest any alien in the United States if the immigration officer has reason to believe that the alien is in the United States in violation of any such law or regulation and is likely to escape before a warrant can be obtained for his or her arrest. When making an arrest, the designated immigration officer shall adhere to the provisions of the enforcement standard governing the conduct of arrests in § 287.8(c).

(ii) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the arrest power conferred by section 287(a)(2) of the Act:

- (A) Border patrol agents, including aircraft pilots;
- (B) Special agents;
- (C) Deportation officers;
- (D) Immigration inspectors;
- (E) Immigration examiners;
- (F) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(G) Immigration officers who need the authority to arrest aliens under section 287(a)(2) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner.

(2) *Arrests of persons under section 287(a)(4) of the Act for felonies regulating the admission, exclusion, or expulsion of aliens.* (i) Section 287(a)(4) of the Act authorizes designated immigration officers, as listed in paragraph (c)(2)(ii) of this section, to arrest persons, without warrant, for felonies that have been committed and that are cognizable under any law of the United States regulating the admission, exclusion, or expulsion of aliens, if the immigration officer has reason to believe that the person is guilty of such felony and if there is a likelihood of the person escaping before a warrant can be obtained for his or her arrest. When making an arrest, the designated immigration officer shall adhere to the provisions of the enforcement standard governing the conduct of arrests in § 287.8(c) of this part.

(ii) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to

exercise the arrest power conferred by section 287(a)(4) of the Act:

- (A) Border patrol agents, including aircraft pilots;
- (B) Special agents;
- (C) Deportation officers;
- (D) Immigration inspectors;
- (E) Immigration examiners;
- (F) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(G) Immigration officers who need the authority to arrest persons under section 287(a)(4) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner with the approval of the Deputy Attorney General.

(3) *Arrests of persons under section 287(a)(5)(A) of the Act for any offense against the United States.* (i) Section 287(a)(5)(A) of the Act authorizes designated immigration officers, as listed in paragraph (c)(3)(ii) of this section, to arrest persons, without warrant, for any offense against the United States if the offense is committed in the immigration officer's presence while the immigration officer is performing duties relating to the enforcement of the immigration laws at the time of the arrest and there is a likelihood of the person escaping before a warrant can be obtained for his or her arrest. When making an arrest, the designated immigration officer shall adhere to the provisions of the enforcement standard governing the conduct of arrests in § 287.8(c).

(ii) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the arrest power conferred by section 287(a)(5)(A) of the Act:

- (A) Border patrol agents, including aircraft pilots;
- (B) Special agents;
- (C) Deportation officers;
- (D) Immigration inspectors (permanent full-time immigration inspectors only);

(E) Immigration examiners when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections;

(F) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(G) Immigration officers who need the authority to arrest persons under section 287(a)(5)(A) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the

Commissioner with the approval of the Deputy Attorney General.

(4) *Arrests of person under section 287(a)(5)(B) of the Act for any felony.* (i) Section 287(a)(5)(B) of the Act authorizes designated immigration officers, as listed in paragraph (c)(4)(iii) of this section, to arrest persons, without warrant, for any felony cognizable under the laws of the United States if:

(A) The immigration officer has reasonable grounds to believe that the person to be arrested has committed or is committing such a felony;

(B) The immigration officer is performing duties relating to the enforcement of the immigration laws at the time of the arrest;

(C) There is a likelihood of the person escaping before a warrant can be obtained for his or her arrest; and

(D) The immigration officer has been certified as successfully completing a training program which covers such arrests and the standards with respect to the enforcement activities of the Service as defined in § 287.8.

(ii) When making an arrest, the designated immigration officer shall adhere to the provisions of the enforcement standard governing the conduct of arrests in § 287.8(c).

(iii) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the arrest power conferred by section 287(a)(5)(B) of the Act:

(A) Border patrol agents, including aircraft pilots;

(B) Special agents;

(C) Deportation officers;

(D) Immigration inspectors (permanent full-time immigration inspectors only);

(E) Immigration examiners when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections;

(F) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(G) Immigration officers who need the authority to arrest persons under section 287(a)(5)(B) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner with the approval of the Deputy Attorney General.

(iv) Notwithstanding the authorization and designation set forth in paragraph (c)(4)(iii) of this section, no immigration officer is authorized to make an arrest for any felony under the

authority of section 287(a)(5)(B) of the Act until such time as he or she has been certified by the Director of Training as successfully completing a training course encompassing such arrests and the standards for enforcement activities as defined in § 287.8 of this part. Such certification shall be valid for the duration of the immigration officer's continuous employment, unless it is suspended or revoked by the Commissioner or the Commissioner's designee for just cause.

(5) *Arrests of persons under section 274(a) of the Act who bring in, transport, or harbor certain aliens, or induce them to enter.* (i) Section 274(a) of the Act authorizes designated immigration officers, as listed in paragraph (c)(5)(ii) of this section, to arrest persons who bring in, transport, or harbor aliens, or induce them to enter the United States in violation of law. When making an arrest, the designated immigration officer shall adhere to the provisions of the enforcement standard governing the conduct of arrests in § 287.8(c).

(ii) The following immigration officers who have successfully completed basic immigration law enforcement training are authorized and designated to exercise the arrest power conferred by section 274(a) of the Act:

(A) Border patrol agents, including aircraft pilots;

(B) Special agents;

(C) Deportation officers;

(D) Immigration inspectors;

(E) Immigration examiners when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections;

(F) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(G) Immigration officers who need the authority to arrest persons under section 274(a) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner with the approval of the Deputy Attorney General.

(6) *Custody and transportation of previously arrested persons.* In addition to the authority to arrest pursuant to a warrant of arrest in paragraph (e)(2)(i) of this section, detention enforcement officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to take and maintain custody of and transport any person who has been arrested by an immigration officer pursuant to

paragraphs (c)(1) through (c)(5) of this section.

(d) *Power and authority to conduct searches.* (1) Section 287(c) of the Act authorizes designated immigration officers, as listed in paragraph (d)(2) of this section, to conduct a search, without warrant, of the person and of the personal effects in the possession of my person seeking admission to the United States if the immigration officer has reasonable cause to suspect that grounds exist for exclusion from the United States under the Act that would be disclosed by such search.

(2) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the power to conduct searches conferred by section 287(c) of the Act:

(i) Border patrol agents, including aircraft pilots;

(ii) Special agents;

(iii) Deportation officers;

(iv) Immigration inspectors;

(v) Immigration examiners;

(vi) Supervisory and managerial

personnel who are responsible for supervising the activities of those officers listed above; and

(vii) Immigration officers who need the authority to conduct searches under section 287(c) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner.

(e) *Power and authority to execute warrants.* (1) *Search warrants.* The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the power conferred by section 287(a) of the Act to execute a search warrant:

(i) Border patrol agents, including aircraft pilots;

(ii) Special agents;

(iii) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above, and

(iv) Immigration officers who need the authority to execute search warrants under section 287(a) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner with the approval of the Deputy Attorney General.

(2) *Arrest warrants.* (1) *Immigration violations.* The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the power pursuant to section 287(a) of

the Act to execute warrants of arrest for administrative immigration violations issued under section 242 of the Act or to execute warrants of criminal arrest issued under the authority of the United States:

- (A) Border patrol agents, including aircraft pilots;
- (B) Special agents;
- (C) Deportation officers;
- (D) Detention enforcement officers (warrants of arrest for administrative immigration violations only);
- (E) Immigration inspectors;
- (F) Immigration examiners when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections;
- (G) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(H) Immigration officers who need the authority to execute arrest warrants for immigration violations under section 287(a) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner, for warrants of arrest for administrative immigration violations, and with the approval of the Deputy Attorney General, for warrants of criminal arrest.

(ii) *Non-immigration violations.* The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the power to execute warrants of criminal arrest for non-immigration violations issued under the authority of the United States:

- (A) Border patrol agents, including aircraft pilots;
- (B) Special agents;
- (C) Deportation officers;
- (D) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(E) Immigration officers who need the authority to execute warrants of arrest for non-immigration violations under section 287(a) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner with the approval of the Deputy Attorney General.

(f) *Power and authority to carry firearms.* The following immigration officers who have successfully completed basic immigration enforcement training are hereby authorized and designated to exercise the power conferred by section 287(a) of the Act to carry firearms provided that they are individually qualified by

training and experience to handle and safely operate the firearms they are permitted to carry, maintain proficiency in the use of such firearms, and adhere to the provisions of the enforcement standard governing the use of force in § 287.8(a):

- (1) Border patrol agents, including aircraft pilots;
- (2) Special agents;
- (3) Deportation officers;
- (4) Detention enforcement officers;
- (5) Immigration inspectors;
- (6) Immigration examiners when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections;
- (7) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and
- (8) Immigration officers who need the authority to carry firearms under section 287(a) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner with the approval of the Deputy Attorney General.

9. Section 287.7 is amended by revising paragraph (a)(1) to read as follows:

§ 287.7 Detainer provisions under section 287(d)(3) of the Act.

(a) *Detainers in general.* (1) A detainer may be issued only in the case of an alien who there is reason to believe is amenable to exclusion or deportation proceedings under any provision of law. The following immigration officers are hereby authorized to issue detainers under section 287(d)(3) of the Act:

- (i) Border patrol agents, including aircraft pilots;
- (ii) Special agents;
- (iii) Deportation officers;
- (iv) Immigration inspectors;
- (v) Immigration examiners;
- (vi) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(vii) Immigration officers who need the authority to issue detainers under section 287(d)(3) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner.

* * * * *

10. Part 287 is amended by adding §§ 287.8, 287.9, 287.10, and 287.11 to read as follows:

§ 287.8 Standards for enforcement activities.

The following standards for enforcement activities contained in this

section must be adhered to by every immigration officer involved in enforcement activities. Any violation of this section shall be reported pursuant to § 287.10.

(a) *Use of force.* (1) *Non-deadly force.* (i) Non-deadly force is any use of force other than that which is considered deadly force as defined in paragraph (a)(2) of this section.

(ii) Non-deadly force may be used only when a designated immigration officer, as listed in paragraph (a)(1)(iv) of this section, has reasonable grounds to believe that such force is necessary.

(iii) A designated immigration officer shall always use the minimum non-deadly force necessary to accomplish the officer's mission and shall escalate to a higher level of non-deadly force only when such higher level of force is warranted by the actions, apparent intentions, and apparent capabilities of the suspect, prisoner, or assailant.

(iv) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to exercise the power conferred by section 287(a) of the Act to use non-deadly force should circumstances warrant it:

- (A) Border patrol agents, including aircraft pilots;
- (B) Special agents;
- (C) Deportation officers;
- (D) Detention enforcement officers;
- (E) Immigration inspectors;
- (F) Immigration examiners when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections;
- (G) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and

(H) Immigration officers who need the authority to use non-deadly force under section 287(a) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner.

(2) *Deadly force.* (i) Deadly force is any use of force that is likely to cause death or serious bodily harm.

(ii) Deadly force may be used only when a designated immigration officer, as listed in paragraph (a)(2)(iii) of this section, has reasonable grounds to believe that such force is necessary to protect the designated immigration officer or other persons from the present danger of death or serious bodily harm.

(iii) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby

authorized and designated to exercise the power conferred by section 287(a) of the Act to use deadly force should circumstances warrant it:

- (A) Border patrol agents, including aircraft pilots;
- (B) Special agents;
- (C) Deportation officers;
- (D) Detention enforcement officers;
- (E) Immigration inspectors;
- (F) Immigration examiners when in the uniform of an immigration inspector and performing inspections or supervising other immigration inspectors performing inspections;
- (G) Supervisory and managerial personnel who are responsible for supervising the activities of those officers listed above; and
- (H) Immigration officers who need the authority to use deadly force under section 287(a) of the Act in order to effectively accomplish their individual missions and who are designated, individually or as a class, by the Commissioner with the approval of the Deputy Attorney General.

(b) *Interrogation and detention not amounting to arrest.* (1) Integration is questioning designed to elicit specific information. An immigration officer, like any other person, has the right to ask questions of anyone as long as the immigration officer does not restrain the freedom of an individual, not under arrest, to walk away.

(2) If the immigration officer has a reasonable suspicion, based on specific articulable facts, that the person being questioned is, or is attempting to be, engaged in an offense against the United States or is an alien illegally in the United States, the immigration officer may briefly detain the person for questioning.

(3) Information obtained from this questioning may provide the basis for a subsequent arrest, which must be effected only by a designated immigration officer, as listed in § 287.5(c). The conduct of arrests is specified in paragraph (c) of this section.

(c) *Conduct of arrests.* (1) *Authority.* Only designated immigration officers are authorized to make an arrest. The list of designated immigration officers varies depending on the type of arrest as listed in § 287.5(c)(1) through (c)(5).

(2) *General procedures.* (i) An arrest shall be made only when the designated immigration officer has reason to believe that the person to be arrested has committed an offense against the United States or is an alien illegally in the United States.

(ii) A warrant of arrest shall be obtained whenever possible prior to the arrest.

(iii) At the time of the arrest, the designated immigration officer shall, as soon as it is practical and safe to do so:

(A) Identify himself or herself as an immigration officer who is authorized to execute an arrest; and

(B) State that the person is under arrest and the reason for the arrest.

(iv) With respect to an alien arrested and administratively charged with being in the United States in violation of law, the arresting officer shall adhere to the procedures set forth in § 287.3 if the arrest is made without a warrant, and to the procedures set forth in § 242.2(c)(2) of this chapter if the arrest is made with a warrant.

(v) With respect to a person arrested and charged with a criminal violation of the laws of the United States, the arresting officer shall advise the person of the appropriated rights as required by law at the time of the arrest, or as soon thereafter as practicable. It is the duty of the immigration officer to assure that the warnings are given in a language the subject understands, and that the subject acknowledges that the warnings are understood. The fact that a person has been advised of his or her rights shall be documented on appropriate Service forms and made a part of the arrest record.

(vi) Every person arrested and charged with a criminal violation of the laws of the United States shall be brought without unnecessary delay before a United States magistrate judge, a United States district judge or, if necessary, a judicial officer empowered in accordance with 18 U.S.C. 3041 to commit persons charged with such crimes. Accordingly, the immigration officer shall contact an Assistant United States Attorney to arrange for an initial appearance.

(vii) The use of threats, coercion, or physical abuse by the designated immigration officer to induce a suspect to waive his or her rights or to make a statement is prohibited.

(d) *Transportation.* (1) *Vehicle transportation.* All persons will be transported in a manner that ensures the safety of the persons being transported. When persons arrested or detained are being transported by vehicle, each person will be searched as thoroughly as circumstances permit before being placed in the vehicle. The person being transported shall not be handcuffed to the frame or any part of the moving vehicle or an object in the moving vehicle. The person being transported shall not be left unattended during transport unless the immigration officer needs to perform a law enforcement function.

(2) *Airline transportation.* The escorting officer(s) must abide by all Federal Aviation Administration and airline carrier rules and regulations pertaining to weapons and the transportation of prisoners.

(e) *Vehicular pursuit.* (1) A vehicular pursuit is an active attempt by a designated immigration officer, as listed in paragraph (e)(2) of this section, in a designated pursuit vehicle to apprehend fleeing suspects who are attempting to avoid apprehension. A designated pursuit vehicle is defined as a vehicle equipped with emergency lights and siren, placed in or on the vehicle, that emit audible and visual signals in order to warn others that emergency law enforcement activities are in progress.

(2) The following immigration officers who have successfully completed basic immigration law enforcement training are hereby authorized and designated to initiate a vehicular pursuit:

(i) Border patrol agents, including aircraft pilots;

(ii) Supervisory personnel who are responsible for supervising the activities of those officers listed above; and

(iii) Immigration officers who need the authority to initiate a vehicular pursuit in order to effectively accomplish their individual mission and who are designated, individually or as a class, by the Commissioner.

(f) *Site inspections.* (1) Site inspections are Service enforcement activities undertaken to locate and identify aliens illegally in the United States, or aliens engaged in unauthorized employment, at locations where there is a reasonable suspicion, based on articulable facts, that such aliens are present.

(2) An immigration officer may not enter into the non-public areas of a business, a residence including the curtilage of such residence, or a farm or other outdoor agricultural operation, except as provided in section 287(a)(3) of the Act, for the purpose of questioning the occupants or employees concerning their right to be or remain in the United States unless the officer has either a warrant or the consent of the owner or other person in control of the site to be inspected. When consent to enter is given, the immigration officer must note on the officer's report that consent was given and, if possible, by whom consent was given. If the immigration officer is denied access to conduct a site inspection, a warrant may be obtained.

(3) Adequate records must be maintained noting the results of every site inspection, including those where no illegal aliens are located.

(4) Nothing in this section prohibits an immigration officer from entering into any area of a business or other activity to which the general public has access or onto open fields that are not farms or other outdoor agricultural operations without a warrant, consent, or any particularized suspicion in order to question any person whom the officer believes to be an alien concerning his or her right to be or remain in the United States.

§ 287.9 Criminal search warrant and firearms policies.

(a) A search warrant should be obtained prior to conducting a search in a criminal investigation unless a specific exception to the warrant requirement is authorized by statute or recognized by the courts. Such exceptions may include, for example, the consent of the person to be searched, exigent circumstances, searches incident to a lawful arrest, and border searches. The Commissioner shall promulgate guidelines governing officers' conduct relating to search and seizure.

(b) In using a firearm, an officer shall adhere to the standard of conduct set forth in § 287.8(a)(2). An immigration officer may carry only firearms (whether Service issued or personally owned) that have been approved pursuant to guidelines promulgated by the Commissioner. The Commissioner shall promulgate guidelines with respect to:

(1) Investigative procedures to be followed after a shooting incident involving an officer;

(2) Loss or theft of an approved firearm;

(3) Maintenance of records with respect to the issuance of firearms and ammunition; and

(4) Procedures for the proper care, storage, and maintenance of firearms, ammunition, and related equipment.

§ 287.10 Expedited internal review process.

(a) *Violations of standards for enforcement activities.* Alleged violations of the standards for enforcement activities established in accordance with the provisions of § 287.8 shall be investigated expeditiously consistent with the policies and procedures of the Office of Professional Responsibility and the Office of the Inspector General of the Department of Justice and pursuant to guidelines to be established by the Attorney General. Within the Immigration and Naturalization Service, the Office of Internal Audit is responsible for coordinating the reporting and disposition of allegations.

(b) *Complaints.* Any persons wishing to lodge a complaint pertaining to violations of enforcement standards contained in § 287.8 may contact the Department of Justice, P.O. Box 27606, Washington, DC, 20038-7606, or telephone 1-800-869-4499.

(c) *Expedited processing of complaints.* When an allegation or complaint of violation of § 287.8 is lodged against an employee or officer of the Service, the allegation or complaint shall be referred promptly for investigation in accordance with the policies and procedures of the Department of Justice. At the conclusion of an investigation of an allegation or complaint of violation of § 287.8, the investigative report shall be referred promptly for appropriate action in accordance with the policies and procedures of the Department of Justice.

(d) *Unsubstantiated complaints.* When an investigative report does not support the allegation, the employee or officer against whom the allegation was made shall be informed in writing that the matter has been closed as soon as practicable. No reference to the

allegation shall be filed in the official's or employee's official personnel file.

(e) *Jurisdiction of other Department of Justice organizations.* Nothing in this section alters or limits, is intended to alter or limit, or shall be construed to alter or limit, the jurisdiction or authority conferred upon the Office of the Inspector General, the Office of Professional Responsibility, the Federal Bureau of Investigation, the United States Attorneys, the Criminal Division or the Civil Rights Division, or any other component of the Department of Justice, or any other order of the Department of Justice establishing policy or procedures for the administration of standards of conduct within the Department of Justice.

§ 287.11 Scope.

With regard to this part, these regulations provide internal guidance on specific areas of law enforcement authority. These regulations do not, are not intended to, and shall not be construed to exclude, supplant, or limit otherwise lawful activities of the Immigration and Naturalization Service or the Attorney General. These regulations do not, are not intended to, shall not be construed to, and may not be relied upon to create any rights, substantive or procedural, enforceable at law by any party in any matter, civil or criminal. The Attorney General shall have exclusive authority to enforce these regulations through such administrative and other means as he or she may deem appropriate.

Dated: August 7, 1994.

Janet Reno,

Attorney General.

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