NIOSH

CRITERIA FOR A RECOMMENDED STANDARD....
OCCUPATIONAL EXPOSURE TO

# DINITRO-ORTHO-CRESOL

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

# criteria for a recommended standard....

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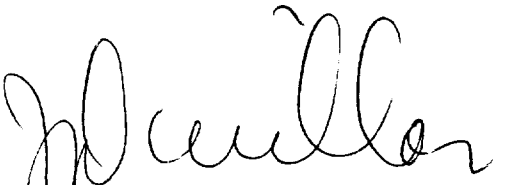
# PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on dinitro-ortho-cresol by members of the NIOSH staff and the valuable constructive comments by the Review Consultants on Dinitro-ortho-Cresol, by the ad hoc committee of the American Conference of Govermental Industrial

Hygienists, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on dinitro-ortho-cresol. A list of Review Consultants appears on page vi. A list of review consultants and a list of the federal agencies to which the document was submitted are given on pages vi and vii.



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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and recommended standard for dinitro-ortho-cresol. David J. Brancato of this Division served as criteria manager. SRI International developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31.

The Division review of this document was provided by Douglas L. Smith, Ph.D. (Chairman), Jon R. May, Ph.D., and Richard A. Rhoden, Ph.D, with Larry K. Lowry, Ph.D. (Division of Biomedical and Behavioral Science), Harry M. Donaldson (Division of Surveillance, Hazard Evaluations, and Field Studies), and Charles C. Hassett, Ph.D.

The views expressed and conclusions reached in this document, together with the recommendations for a standard, are those of NIOSH. These views and conclusions are not necessarily those of the consultants, other federal agencies or professional societies that reviewed the document, or of the contractor.

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Department of Health, Education, and Welfare
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    National Institute of Neurological and Communicative Diseases and Strokes

Consumer Product Safety Commission
  Bureau of Biomedical Science

Energy Research and Development Administration
  Division of Safety Standards and Compliance

Environmental Protection Agency
  Health Effects Research Laboratory
  Office of Research and Development

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# I. RECOMMENDATIONS FOR A DINITRO-ORTHO-CRESOL STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to dinitro-ortho-cresol in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the standard should prevent adverse effects of dinitro-ortho-cresol on the health and safety of employees. The standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. Although the workplace environmental limit is considered a safe level based on current information, it should be regarded as the upper boundary of exposure, and every effort should be made to maintain the exposure at levels as low as is technically feasible. The criteria and standards will be subject to review and revision as necessary.

The criteria and recommendations for dinitro-ortho-cresol, which is referred to as DNOC throughout this document, apply to exposure of employees to any DNOC ($C_7H_6N_2O_5$) isomer or to any of the salts of DNOC. The 4,6 isomer of DNOC is the most commercially important one. DNOC is used primarily as a blossom-thinning agent on fruit trees and as a fungicide, insecticide, and miticide on fruit trees during the dormant season.

An evaluation of the literature indicates that occupational injury and disease associated with exposure to DNOC are caused primarily by

inhalation of and skin contact with the aerosol form. The recommended environmental limit is based on data that indicate that exposure to DNOC may cause severe increases in the basal metabolic rate (BMR) and central nervous system (CNS) disturbances.

"Occupational exposure" to DNOC, because of systemic effects, absorption through the skin on contact, and possible dermal irritation, is defined as work in any area where DNOC is manufactured, formulated, processed, stored, or otherwise used. The "action level" is defined as one-half the recommended time-weighted average (TWA) environmental limit. Adherence to all provisions of the standard is required if any employee is exposed to airborne DNOC at concentrations above the action level. If any employee is occupationally exposed at concentrations equal to or below the action level, then all sections of the recommended standard except Sections 4(c)(2) and 8(a) shall be complied with because adverse effects can be produced by skin and eye contact. If exposure to other chemicals also occurs, provisions of any applicable standards for the other chemicals shall also apply.

Section 1 - Environmental (Workplace Air)

(a) Concentration

When skin exposure is prevented, occupational exposure to DNOC shall be controlled so that no employee is exposed to DNOC at a concentration greater than 0.2 milligrams per cubic meter (mg/cu m) of air, determined as a time-weighted average (TWA) concentration for up to a 10-hour workshift and 40-hour workweek.

(b) Sampling and Analysis

Procedures for the collection and analysis of environmental samples shall be as provided in Appendices I and II or by any other methods shown to be at least equivalent in precision, accuracy, and sensitivity to the methods specified.

Section 2 - Medical

(a) Medical Examinations

Medical surveillance shall be made available as outlined below to all employees subject to occupational exposure to DNOC.

(1) Preplacement examinations shall include at least:

(A) Comprehensive medical and work histories with special emphasis directed to any preexisting disorders, particularly of the lungs, liver, kidneys, thyroid gland, nervous and cardiovascular systems, skin, and eyes.

(B) A physical examination giving special attention to the lungs, liver, kidneys, nervous and cardiovascular systems, skin, and eyes.

(C) A urinalysis that includes a microscopic examination. Additional tests, such as a complete blood count, hematocrit, and liver and kidney function tests, should be considered by the responsible physician.

(D) An evaluation of the worker's ability to use positive and negative pressure respirators.

(2) Periodic examinations shall be made available on at least an annual basis. These examinations shall include at least:

(A) Interim medical and work histories.

(B) A physical examination as described in (1)(B) and (C) of this section.

(C) Clinical tests including at least those described above for the preplacement examination.

(3) Employees displaying signs or symptoms that may be associated with a generalized increase in metabolic rate shall be medically evaluated.

(4) Initial medical examinations shall be made available to all workers as soon as practicable after promulgation of a standard based on these recommendations.

(5) Employees and potential employees having medical conditions, such as disorders of the cardiovascular and respiratory systems, that would be directly or indirectly aggravated by exposure to DNOC shall be counseled on the increased risk of impairment of their health from working with these substances. All employees occupationally exposed to DNOC shall be informed about the value of periodic medical examinations.

(6) In an emergency involving DNOC, such as an employee's clothing becoming wetted with DNOC solution, or if an employee exhibits an array of signs and symptoms consistent with possible DNOC intoxication, affected personnel shall be given immediate first aid, followed by prompt medical evaluation and care. In the event of skin or eye contact with liquid DNOC, contaminated clothing and shoes shall be removed immediately, and skin and eyes shall be flushed with copious amounts of water. In all cases of splashes, spills, or leaks where significant skin or eye contact with or inhalation of the materials occurs appropriate medical personnel

shall be notified. Medical attendants shall be informed of the possibility of systemic effects, and the persons so exposed shall be observed for a minimum of 72 hours. Medical examinations should be made available as warranted by the results of the 72-hour observation period.

(7) Pertinent medical records, including biologic monitoring data, shall be maintained by the employer for all employees occupationally exposed to DNOC. Such records shall be retained for at least 30 years after termination of employment. Records of environmental exposures applicable to an employee shall be included in the employee's medical records and shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

(b) Biologic Monitoring

(1) Biologic monitoring shall be provided to all employees engaged in the following agriculturally related occupations: mixers, loaders, ground and aerial applicators, and flaggers. This monitoring shall consist of weekly sampling and analysis of workers' blood for DNOC content during the period of expected exposure. Measurements shall be taken as close as feasible to, but no sooner than, 8 hours after the weekly exposure ends. Such monitoring shall be performed to ensure that no worker absorbs an unacceptable amount of the compound. Unacceptable absorption of DNOC, indicating a failure of control procedures or work practices, is demonstrated when the DNOC concentration equals or exceeds 20 $\mu$g/g of whole blood. Any employee whose blood DNOC concentration exceeds 10 $\mu$g/g of whole blood, the "warning" level, shall be advised of this finding, and an

industrial hygiene survey shall be conducted in the workplace of the affected employee unless the cause of the exposure is known and corrective action has been initiated. This survey shall include an assessment of the potential for dermal exposure. Based on the results of this survey, necessary corrective action shall be taken. Any employee whose whole blood DNOC concentration equals or exceeds 20 μg/g shall be removed from potential exposure to DNOC and placed under medical observation (see paragraph (2) below). In such cases, provisions for an industrial hygiene survey and decisions for possible corrective action shall be as previously prescribed for DNOC concentrations of 10 μg/g of whole blood.

(2) An employee who has been removed from DNOC exposure shall not be allowed to return to work involving occupational DNOC exposure until the concentration of DNOC in the blood is less than 20 μg/g, unless the responsible physician has approved the employee's return.

(3) Procedures for collection and analysis of whole blood for DNOC shall be as provided in Appendix III or by any method shown to be at least equivalent in accuracy, precision, and sensitivity to those specified.

Section 3 - Labeling and Posting

All labels and warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Illiterate workers and workers reading languages other than those used on labels and posted signs shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs.

(a) Labeling

All bulk containers that hold DNOC shall carry, in a readily visible location, a label that bears the trade name of the product and information on the effects of exposure to the compound on human health. The information shall be arranged as in the example below.

DINITRO-ORTHO-CRESOL
(Trade Name)

DANGER!

MAY BE FATAL IF INHALED,
ABSORBED THROUGH SKIN,
OR INGESTED

Avoid breathing vapor or aerosol.
Do not get on skin, in eyes or mouth, or on clothing.
Keep containers closed when not in use.
Use only with adequate ventilation.

First Aid: Call a physician immediately. In case of skin or eye contact, immediately remove contaminated clothing and flush skin or eyes with large amounts of water for at least 15 minutes. If material is inhaled, remove victim to fresh air. If victim is not breathing, give artificial respiration. If breathing is difficult, give oxygen. If swallowed, induce vomiting.

NOTE TO PHYSICIAN: Compound is a metabolic stimulant. Treat symptomatically.

(b) Posting

In all manufacturing, formulating, and storage areas where occupational exposure to DNOC can occur, signs containing health hazard warning statements appropriate for DNOC shall be posted in readily visible locations. This information shall be arranged as in the example below.

DANGER!

DINITRO-ORTHO-CRESOL PRESENT IN AREA

MAY BE FATAL IF ABSORBED THROUGH
SKIN, INHALED, OR INGESTED

Avoid breathing vapor or aerosol.
Do not get on skin, in eyes or mouth, or on clothing.

(c) If respirators are required, the following statement shall be added in large letters to the signs required in Section 3(b):

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

(d) In any area where there is a likelihood of emergency situations arising, signs required by Section 3(b) shall be supplemented with signs giving emergency and first-aid instructions and procedures, the location of first-aid supplies and emergency equipment, and the locations of emergency showers and eyewash fountains.

Section 4 - Personal Protective Equipment

Engineering controls and safe work practices shall be used when needed to keep concentrations of airborne DNOC at or below the prescribed limit and to minimize skin and eye contact with DNOC. In addition, employers shall provide protective equipment and clothing to employees when necessary.

(a) Eye Protection

Safety glasses, chemical safety goggles, or face shields (8-inch minimum) with goggles shall be provided by the employer and shall be worn during any operation in which DNOC may contact the eyes (29 CFR 1910.133).

(b) Skin Protection

(1) Unless separately provided in this section, any employees who engage in filling, pouring, mixing, formulating, loading, applying, or otherwise handling DNOC (including open-system manufacturing processes) shall be provided with protective head coverings, face shields (8-inch minimum) with goggles, gloves, full-body coveralls, aprons, rainsuits, and footwear, and these shall be worn when needed to prevent skin contact with DNOC. Gloves should have reverse guantlets and coveralls should be made of a closely-woven material (nylon or cotton fabric is especially protective).

(2) Employees handling sealed containers of DNOC shall be provided with and required to wear full-body coveralls and gloves.

(3) Employees applying DNOC by closed-cockpit aircraft or by enclosed motor vehicles with air-conditioned cabins shall be provided with gloves. Employees applying DNOC by open-cockpit aircraft shall be provided with and required to wear full-body coveralls, safety goggles, and gloves, and to carry a portable emergency eyewash bottle.

(4) Employees acting as flaggers (other than those flagging from enclosures) in the aerial application of DNOC shall be provided with and required to wear full-body coveralls or rainsuits, protective head and neck coverings, gloves, safety goggles, and footwear.

(5) Where toxic residues present a reasonable potential for exposure, employees entering areas treated with DNOC shall be provided with, and required to wear, gloves, full-body coveralls or rainsuits, face shields if foliage is likely to contact the face, and footwear.

(6) Employees, such as cleanup personnel, entering areas contaminated with DNOC shall be provided with, and required to wear, gloves, full-body coveralls or rainsuits, footwear, aprons, and such other personal protective equipment as may be required for adequate protection against the particular hazards presented.

(7) Clothing contaminated with DNOC shall be either disposed of or cleaned before reuse. Anyone handling contaminated clothing or responsible for its cleaning shall be instructed as to the hazards, relevant symptoms of overexposure, appropriate emergency procedures, and proper conditions and precautions for the safe handling and use of DNOC.

(8) The employer shall ensure that all personal protective devices are inspected regularly and maintained in clean and satisfactory working condition.

(c) Respiratory Protection

(1) The use of respirators to achieve compliance with the recommended exposure limit is permitted only:

(A) During the time necessary to install or test the required engineering controls.

(B) During emergencies or during nonroutine operations, such as maintenance or repair activities, when air concentrations of DNOC may exceed the permissible environmental limit.

(2) When use of a respirator is permitted, it shall be selected and used pursuant to the following requirements:

(A) The employer shall establish and enforce a respiratory protective program meeting the requirements of 29 CFR 1910.134.

(B) The employer shall provide respirators in accordance with Table I-1 and shall ensure that the employee uses the respirator provided when necessary. The respiratory protective devices provided in conformance with Table I-1 shall comply with the standards jointly approved by NIOSH and the Mining Enforcement and Safety Administration (MESA) as specified under the provisions of 30 CFR 11.

(C) Respirators specified for use in high concentrations of DNOC may be used in atmospheres of lower concentrations.

(D) The employer shall ensure that respirators are adequately cleaned and maintained and that employees are trained and drilled at least annually in the proper use and testing for leakage of respirators assigned to them.

(E) Respirators shall be easily accessible, and employees shall be informed of their location.

Section 5 - Informing Employees of Hazards

(a) Employees working in an area that may involve occupational exposure to DNOC shall be verbally informed of the hazards of such employment, the symptoms associated with exposure to this substance, the appropriate emergency procedures to use, and the proper procedures for the safe handling and use of DNOC.

TABLE I-1

RESPIRATOR SELECTION GUIDE
FOR DNOC MANUFACTURERS, FORMULATORS, AND FIELD WORKERS

| Concentration | Respirator Type Approved under Provisions of 30 CFR 11 |
|---|---|
| Equal to or less than 5 mg/cu m | (1) Full facepiece respirator equipped with a combination organic vapor cartridge and high-efficiency filter<br>(2) Powered air-purifying respirator with full facepiece, helmet, or hood, equipped with a combination organic vapor cartridge and high-efficiency filter<br>(3) Supplied-air respirator with full facepiece, hood, or helmet<br>(4) Supplied-air impervious suit<br>(5) Self-contained breathing apparatus with full facepiece, operated in demand (negative pressure) mode |
| Greater than 5 mg/cu m | (1) Self-contained breathing apparatus with full facepiece, operated in pressure-demand or other positive pressure mode<br>(2) Combination Type C supplied-air respirator with full facepiece and auxiliary self-contained air supply, operated in pressure-demand mode |
| Emergency (entry into area of unknown concentration) | (1) Self-contained breathing apparatus with full facepiece, operated in pressure-demand or other positive pressure mode<br>(2) Combination Type C supplied-air respirator with full facepiece and auxiliary self-contained air supply, operated in pressure-demand mode |
| Firefighting | Self-contained breathing apparatus with full facepiece, operated in pressure-demand or other positive pressure mode |

(b) A continuing education program, conducted on at least a yearly basis by qualified health and safety personnel, shall be instituted to ensure that employees whose jobs may involve exposure to DNOC, including those engaged in maintenance and repair, are given current knowledge of job hazards, proper maintenance procedures, and cleanup methods. Employees shall be informed of the general nature of the medical surveillance procedures and why it is advantageous to the workers to undergo these examinations. Each employee shall be told about the availability of the required information, which shall include, as a minimum, that prescribed in paragraph (c) of this section.

(c) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix IV or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor, and shall be kept on file, readily accessible to employees.

Section 6 - Work Practices

Protective clothing and equipment, as set forth in Section 4, shall be worn by all employees engaged in any operation where DNOC may come into contact with the skin or eyes.

(a) Work Practices for Manufacture and Formulation of DNOC

(1) Engineering controls, such as process enclosure or local exhaust ventilation, shall be used as needed to keep airborne concentrations of DNOC within the recommended environmental limit. All such control equipment shall meet the requirements of subpart (s) of 29 CFR 1910 for hazardous vocations.

(2) Equipment and systems used for handling and transferring DNOC shall be enclosed to the extent feasible to prevent skin and eye contact.

(3) Containers of DNOC shall be kept tightly closed at all times when not in use. Storage shall be in well-ventilated areas away from heat and strong oxidizers. Containers shall be periodically inspected for leakage and deterioration.

(4) Written operating instructions and first-aid procedures shall be formulated and posted in areas where DNOC is manufactured, formulated, processed, stored, or otherwise used.

(5) All equipment and systems used for handling and transferring DNOC shall be inspected periodically for leaks. Valves, fittings, and connections shall be checked for tightness and good working order. Needed repairs and adjustments shall be made promptly.

(6) Before maintenance work is started, sources of DNOC shall be eliminated to the extent feasible. If airborne concentrations exceed the recommended environmental limit, respiratory protective equipment as described in Table I-1 shall be required during such maintenance work.

(7) Easily accessible, well-marked emergency showers and eyewash fountains shall be available in all work areas where DNOC is manufactured or formulated. In case of contact, the skin or eyes shall be flushed with large amounts of water for at least 15 minutes.

(8) Clothing that has become contaminated shall be either cleaned before reuse or disposed of. Contaminated clothing shall be kept in properly labeled, closed containers until it is laundered or discarded.

(9) Facilities, such as double lockers, shall be provided for each employee so clean and soiled clothing can be kept separate.

(10) Transportation and use of DNOC shall comply with all federal, state, and local regulations.

(b) Work Practices in the Application of DNOC

(1) Employees handling DNOC concentrates shall work in teams. In addition, regardless of the concentration of the material, all mixers, loaders, flaggers, and applicators must maintain periodic communication with a person capable of summoning emergency aid if needed.

(2) Employees potentially exposed to DNOC while spraying shall remain upwind from the spray whenever possible.

(3) No aerial applicator may mix or load pesticides containing DNOC in whole or in part, unless closed mixing or loading systems are used. This provision allows an aerial applicator to supervise mixing or loading operations involving open systems.

(4) Materials containing DNOC shall not be used when testing mixing, loading, or application equipment for leaks, or when testing for clogged valves, lines, or strainers, or when equipment is calibrated.

(5) Dispersal equipment containing DNOC may not be turned on outside the area to be treated. Except in an emergency, jettison or otherwise dumping of DNOC from application, mixing, or loading vehicles shall be prohibited unless proper disposal procedures are followed.

(6) Employees piloting agricultural aircraft may not fly through the drift of an application, nor shall they start or continue an application if wind creates a drift hazard to themselves or others, nor

shall they spray or dust over waterways, canals, buildings, dwellings, vehicles, or persons, including flaggers.

(7) Employees occupationally exposed to DNOC shall have provided to them in a readily accessible site either 25 gallons of water for each person or 100 gallons, whichever is greater. Motor vehicles shall have at least 20 gallons of water stored in closed containers. Agricultural aircraft shall carry emergency eyewash bottles.

(8) Any emergency or accidental release, eg, application to incorrect field, of DNOC from agricultural aircraft or motor vehicles shall be reported immediately to people resident in the area and to appropriate local regulatory or health officials.

(c) Control of Unit Operations

(1) Controls of unit operations of equivalent or superior effectiveness may be substituted for those specified in paragraphs 2 through 9 below.

(2) All fittings, hoses, tubing, pumps, valves, and associated equipment operated at positive pressure shall be sufficient to withstand 2.5 times the maximum pressure and tested at least weekly for leaks and other signs of deterioration.

(3) All hoses, pipes, and tubing used for filling tanks on loading or application vehicles with DNOC shall be equipped with quick-acting shutoff valves or other devices at the discharge ends to prevent dripping.

(4) Back siphoning by hoses used for filling vessels, tanks, or other containers with DNOC or for adding any other liquid shall not be permitted if the container already contains DNOC.

(5) When positive displacement pumps are used with hoses, pipes, or tubing equipped with shutoff valves at the discharge end, a relief device shall be installed to bypass liquid back to the low-pressure side of the system to prevent rupture of hoses, pipes, tubing, or pumps.

(6) All application equipment with one or more nozzles shall have the distribution manifold shielded to minimize operator exposure in the event of malfunction.

(7) Opaque tanks used for mixing, loading, or applying DNOC shall be equipped with indicators of the level of liquid within the tank.

(8) Loading equipment shall be fitted with an automatic shutoff device to prevent overfilling.

(9) Tank covers shall be so constructed to minimize the possibility of contents spilling in the event of rollover or aerial accident.

(d) Emergency Procedures

Emergency plans and procedures shall be developed for all work areas where there is a potential for exposure to DNOC. The measures shall include those specified below and any others considered appropriate for a specific operation or process. Employees shall be trained to implement the plans and procedures effectively.

(1) Prearranged plans shall be instituted for obtaining emergency medical care and for the transportation of injured workers. A sufficient number of employees shall be trained in first aid so that assistance is available immediately when necessary.

(2) Spills of DNOC shall be cleaned up immediately. The area of the spill shall be posted and secured. Only authorized personnel,

adequately protected and properly trained, shall be permitted to enter the area to shut off sources of DNOC.

(3) Spilled liquids shall be sorbed with vermiculite, dry sand, earth, or other appropriate material. If sufficient drainage to suitable collection basins is available, spilled liquid shall be hosed away with large quantities of water. Methods of waste disposal shall comply with applicable federal, state, and local regulations.

(e) Confined Spaces

(1) Cleaning, maintenance, and repair of tanks, process equipment, and lines shall be done only by properly trained and adequately protected employees under supervisory control.

(2) Entry into confined spaces, such as tanks, pits, tank cars, barges, and process vessels, shall be controlled by a permit system. Permits shall be signed by an authorized representative of the employer and shall certify that preparation of the confined space, precautionary measures, and personal protective equipment are adequate and that precautions have been taken to ensure that prescribed procedures will be followed.

(3) Before they are entered, confined spaces shall be inspected and tested for oxygen deficiency and for the presence of DNOC and other known or suspected contaminants.

(4) No employee shall enter any confined space that does not have an entry large enough to admit an employee equipped with safety harness, lifeline, and appropriate respiratory equipment.

(5) Personnel entering confined spaces shall wear respirators as specified in Section 4.

(6) Confined spaces shall be ventilated while work is in progress to keep the concentration of airborne DNOC and any other contaminants at or below their recommended environmental limits and to prevent oxygen deficiency.

(7) Anyone entering a confined space shall be observed from the outside by another properly trained and protected worker. An additional supplied-air or self-contained breathing apparatus with safety harness and lifeline shall be located outside the confined space for emergency use. The person entering the confined space shall maintain continuous communication with the standby worker.

Section 7 - Sanitation

(a) Plant sanitation shall meet the requirements of 29 CFR 1910.141.

(b) Food preparation, dispensing (including vending machines), and eating shall be prohibited in areas where DNOC is manufactured, formulated, processed, stored, or otherwise used.

(c) Smoking shall be prohibited in areas where DNOC is manufactured, formulated, processed, stored, or otherwise used.

(d) Employees who handle DNOC shall be instructed to wash their hands thoroughly with soap or mild detergent and water before using toilet facilities or eating.

Section 8 - Monitoring and Recordkeeping Requirements

As soon as practicable after the promulgation of a standard based on these recommendations, employers shall determine by an industrial hygiene survey whether exposure to airborne DNOC is in excess of the action level. Records of these surveys shall be kept, and if an employer concludes that air levels are at or below the action level, the records must show the basis for this conclusion. Surveys shall be repeated at least once every year and within 30 days of any process change likely to result in an increased concentration of airborne DNOC. When the industrial hygiene survey demonstrates that the environmental concentration of DNOC exceeds the action level, the following requirements shall apply:

(a) Personal Monitoring

(1) A program of personal monitoring shall be instituted to identify and measure, or to permit calculation of, the exposure of each employee occupationally exposed to airborne DNOC. Source and area monitoring may be used to supplement personal monitoring.

(2) In all personal monitoring, samples representative of the exposure to airborne DNOC in the breathing zone of the employee shall be collected. Procedures for sampling and analysis of DNOC shall be in accordance with Section 1(b).

(3) For each TWA concentration determination, a sufficient number of samples shall be taken to characterize employee exposures during each workshift. Variations in work and production schedules, as well as employee locations and job functions, shall be considered in decisions on sampling locations, times, and frequencies.

(4) Each operation shall be sampled at least once every 3

months or as otherwise indicated by a professional industrial hygienist. If an employee is found to be exposed at a level in excess of the TWA concentration limit, the exposure of that employee shall be measured at least once every week, control measures shall be initiated, and the employee shall be notified of the exposure and of the control measures being implemented. Such monitoring shall continue until two consecutive determinations, at least 1 week apart, indicate that employee exposure no longer exceeds the environmental limit. Quarterly monitoring shall then be resumed.

(b) Recordkeeping

Records of environmental monitoring shall be kept for at least 30 years. These records shall include the dates and times of measurements, duties and location of the employees within the worksite, sampling and analytical methods used, number, duration, and results of the samples taken, TWA concentrations estimated from these samples, type of personal protective equipment used, if any, and employees' names. These records shall be made available to the designated representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

# II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational disease or injury arising from exposure to DNOC. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, has formalized a system for the development of criteria upon which standards can be established to protect the health and to provide for the safety of employees exposed to hazardous chemical and physical agents. The criteria and recommended standards should enable management and labor to develop better engineering controls resulting in more healthful work environments, and mere compliance with the recommended standards should not be regarded as a final goal.

The criteria and recommended standard for DNOC are part of a continuing series of documents published by NIOSH. The proposed standard applies to the manufacture, formulation, processing, storage, and use of, or other occupational exposure, to DNOC as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any extrapolation beyond the occupational

environment is not warranted. It is intended to protect against the development of systemic toxic effects and local effects on the skin and eyes of employees and be measurable by techniques that are valid, reproducible, and available to industry and governmental agencies.

Occupational exposure to DNOC in the United States occurs primarily to employees involved in the formulation or spraying of DNOC products for agricultural use. Inhalation of the aerosol or vapor is the most common route of occupational exposure, and the subsequent severe stimulation of metabolism and possible effects on the CNS are major reasons for concern about employee exposure to DNOC. Although there is considerable information on the health effects of inhaled DNOC, the concentrations at which it causes intoxication in humans have been investigated in only a few studies, and these studies have inadequately described the health effects. Therefore, further research is needed to elucidate the effects in humans of both short- and long-term exposure to airborne DNOC at concentrations at or below the recommended environmental limit. Since there is evidence that blood DNOC levels are correlated with toxic signs and symptoms, it would be desirable to obtain additional information on the relationship between the concentration of DNOC a person is exposed to and the resultant blood DNOC levels. Experiments to assess the carcinogenic, mutagenic, and teratogenic potential of DNOC are also needed.

# III. BIOLOGIC EFFECTS OF EXPOSURE

## Extent of Exposure

Dinitro-ortho-cresol, $C_7H_6N_2O_5$, is a yellow crystalline solid derived from o-cresol. There are six DNOC isomers, but the 4,6-dinitro isomer (see structure in Figure XIII-1) is the most commercially important. DNOC is produced either by sulfonation of o-cresol followed by treatment with nitric acid or by treatment of o-cresol in glacial acetic acid with nitric acid at low temperatures [1]. Some important chemical and physical properties of DNOC are shown in Table XIII-1 [2-4].

DNOC was introduced in 1892, in its potassium salt form, as the active ingredient of the pesticide "Antinonnin," used for controlling the nun moth [5]. DNOC is still primarily an agricultural chemical, although it has had limited use in the dyestuff industry and for other minor, miscellaneous industrial purposes. Currently, it is used primarily as a blossom-thinning agent for fruit trees and as a fungicide, insecticide, and miticide applied to fruit trees during the dormant season. Its use for these purposes is confined mainly to the Pacific Northwest.

DNOC has been used less in recent years because it is highly toxic to plants in the growing stage and nonselectively kills both desirable and undesirable vegetation. The Environmental Protection Agency has no record of DNOC being currently manufactured in the United States for use as an agricultural chemical. Imports of DNOC have also decreased in recent years; from 217,899 pounds in 1972 to 146,621 pounds in 1973 and then to

30,442 pounds in 1976. Currently, only one company in the United States formulates the sodium salt of DNOC, which is marketed under the trade name Elgetol. They obtain DNOC by importing the product from Japan. According to a spokesman for this company, Elgetol is formulated once a year on a customer-request basis, and only 3-10 workers, at most, are potentially exposed during its production. Another company announced in 1976 that it would discontinue its small-scale production and formulation of DNOC. Pesticide sprayers are therefore the major group with potential occupational exposure to DNOC. In addition to the DNOC sold for agricultural use, a few chemical distributors sell small amounts of technical grade DNOC for laboratory purposes.

NIOSH estimates that 3,000 workers in the United States are potentially exposed to DNOC.

## Historical Reports

First introduced in 1892 for use against the nun moth [5], DNOC began to draw attention in 1925 for its utility in agriculture and horticulture [6]. Since then, several deaths attributed to exposure to DNOC have occurred in various countries. In addition to its use in agriculture, DNOC was introduced in 1933 as an alternative to dinitrophenol (DNP) in the treatment of obesity [7]. However, high doses caused cataracts, blindness, and death in many people, and as a result DNOC was used for this purpose for only a short time.

Dodds and Pope [8], in 1933, observed that DNOC was three times as potent as DNP in elevating the oxygen consumption rate in guinea pigs.

They therefore thought that less DNOC than DNP could be used to increase the basal metabolic rate (BMR) and produce weight loss. In an attempt to find a safe dose for humans, Dodds and Robertson [9] gave DNOC to a number of healthy young adult volunteers, who were of average weight or overweight. A daily oral dose of 3 mg/kg of body weight produced toxic effects by the 3rd day, when the BMR had increased by an average of 50%. By the 4th day, the BMR had increased as much as 100%. The volunteers experienced profuse sweating, lethargy, headache, loss of appetite, and greenish-yellow pigmentation of the conjunctiva. Treatment with DNOC was then stopped, whereupon the signs and symptoms disappeared. In a second experiment, one 3 mg/kg oral dose of DNOC produced a rapid rise in the BMR to 20-30% higher than the preexposure level within 24 hours. The rate returned to normal 4-5 days later. It was found in a third experiment that 50-100 mg/day (0.5-1.0 mg/kg of body weight) was needed to maintain a BMR 30-50% greater than normal, an increase which the authors reported would not be accompanied by toxic signs or symptoms.

Ibrahim et al [10] reported in 1934 adverse effects in people taking DNOC to lose weight. The authors studied 15 people, 8 men and 7 women, aged 17-38 years, who had taken doses of 50 or 100 mg/day for an average of 7 weeks. After the patients had taken DNOC for a few days, they all developed signs and symptoms of DNOC intoxication, including excessive sweating, thirst, fatigue, decreased appetite, and elevated BMR. Their conjunctivae became greenish yellow.

Other investigators [11,12] also observed toxic effects in persons taking DNOC for weight reduction purposes. In 1936, Plotz [11] described effects similar to those reported by Ibrahim et al [10] in three persons

who had each taken between 0.35 and 1.5 mg/kg/day of DNOC for up to 9 weeks. In 1937, Quick [12] reported the development of cataracts and blindness in a woman who had taken DNOC for 3 years and he noted that a number of other people had developed cataracts after taking DNOC.

Hunter [7] wrote that, by 1937, many poisonings and some deaths had resulted from the use of DNOC for weight reduction purposes. He stated that at least three deaths in Great Britain had been caused by overdoses of DNOC and that cataracts and blindness had developed in some patients months after they had stopped taking DNOC. Although he noted that less than 1% of those who were treated with DNOC developed complications, he considered the difficulty of setting a safe dose for each individual to be the reason that its use as an aid to weight loss was discontinued.

In many countries, deaths from DNOC exposure occurred among workers in the plants where it was manufactured [7]. DNOC dust was apparently the most dangerous form because it was readily inhaled and quickly produced effects. Workers experienced excessive sweating, thirst, a feeling of weakness, and loss of weight. During the summer of 1943, 14 poisonings were reported in a factory in Great Britain where DNOC dust was prepared for use against locusts [7]. After local exhaust ventilation and periodic medical examinations were introduced in the factory, only one mild case was reported.

Bidstrup and Payne [6] noted in 1951 that environmental temperature influenced the severity of intoxication in workers exposed to DNOC. They observed that all the reported fatalities attributed to DNOC poisoning in Great Britain between 1946 and 1950 occurred during what the authors considered to be "unusually hot" weather (56-86 F).

Effects on Humans

Other than those reports dealing with its use as a weight-reducing drug [7,10-12], only a few were found in which authors described the effects of DNOC in nonoccupational exposure situations. The relationship between blood DNOC levels and intoxication has been investigated [13], and effects of DNOC ingestion [13,14] and skin contact [13,15,16] have been observed.

Harvey et al [13], in 1951, described the effects of DNOC taken orally by five male volunteers. Each man was given capsules containing 75 mg of pure DNOC daily for 5 consecutive days, amounting to a dose of 0.92-1.27 mg/kg/day. The concentration of DNOC in the blood was measured 30 minutes before and 1, 2, 4, and 6 hours after each dose was taken and then at various intervals up until 40 days later.

The concentration of DNOC in the blood increased for the first 3-4 days and reached concentrations of 15-20 μg/g [13]. After these concentrations (15-20 μg/g) had been attained, additional doses appeared to cause temporary high blood concentrations which were associated with symptoms. The man receiving the largest daily dose (1.27 mg/kg) showed a peak concentration of 40 μg/g after the fifth dose. The man who had been given 0.92 mg/kg/day received additional DNOC on the 6th and 7th days, which caused the blood DNOC level to rise to 40 and then to 48 μg/g on these 2 days. In both of these men, the high blood DNOC levels were associated with symptoms of poisoning, including lassitude, headache, and malaise. Conjunctival staining was seen by the 4th day in all five volunteers. The concentration of DNOC in the blood was temporarily increased in three of the men when they performed 30 minutes of exercise on

the 8th and 9th days. A 2% aqueous solution of DNOC applied to the skin of three men on day 12 also caused a slight rise in the blood DNOC concentration. DNOC was slowly eliminated from the body. It was still detected in the blood (1 μg/g in each of four subjects) 40 days after the final dose was given.

In 1952, Bidstrup et al [17] discussed additional findings that related to their original study [13]. Regarding the human volunteers given DNOC orally, the authors noted that temporary high blood DNOC concentrations were observed only when the blood was sampled less than 8 hours after the last exposure. This phenomenon occurs because DNOC binds with albumin in the blood [13] and is therefore not rapidly distributed to the body tissues. Apparently, significant distribution occurs 8 hours after exposure to DNOC, and blood samples taken after this time lapse show blood DNOC levels that correlate better with observed signs and symptoms of toxicity. The owner of a firm of contract sprayers informed them that one of the earliest signs of DNOC exposure was a "fitter than usual" feeling in the workers [17]. He gave the example of a man who, because he was feeling well, protested being transferred to another job. As a result of this observation, the authors [17] reevaluated their previous observations [13] and found that, on the 3rd or 4th day of the experiment, all of the volunteers had experienced an exaggerated feeling of well-being. At this time their blood DNOC levels were about 20 μg/g. Bidstrup et al [17] commented that the importance of this finding had not been recognized at the time of the experiment, and it was not mentioned in the earlier report [13].

Sovljanski et al [14], in 1971, reported two suicides by ingestion of known amounts of DNOC. One person had swallowed 50 g of DNOC, and the other, 140 g. Analysis of tissue samples revealed DNOC in the stomach, intestines, liver, kidneys, heart, and brain, with the stomach containing the greatest amount. Blood DNOC levels were not reported.

Observations have been recorded on the effects of DNOC after intentional or unintentional dermal contact. Ambrose [15] investigated the effects of cutaneous application of DNOC to humans. A 2% aqueous solution of the sodium salt of DNOC was applied daily for 30 days to the shaved armpits and forearms of two volunteers. Neither local skin irritation nor systemic effects were observed.

In 1974, Buchinskii [16] reported the death of a 4-year-old boy after DNOC was applied to his skin. A rash had been treated with 50 g of an ointment to which DNOC was added by mistake. The child began vomiting 1 hour later and developed a headache. When he was hospitalized 2 hours after the ointment was applied, he was confused, and his skin, sclera, and what was translated as visible mucosa were stained yellow. His pulse rate was 96 beats/minute, and his respiratory rate was 45/minute. Within half an hour, he was unconscious. Tachycardia developed, and moist rales were detected in the lungs. The boy had convulsions, and death followed 3.5 hours after the ointment was applied. An autopsy showed diffuse petechial hemorrhages in the intestinal mucosa and brain and pulmonary edema. Microscopic examination of several tissues revealed capillary congestion in the brain, liver, lungs, intestinal walls, myocardium, and kidneys. An unspecified amount of DNOC was detected in the blood. Analysis of the ointment showed that it contained 25% DNOC.

Several reports of injuries and deaths of workers exposed to DNOC have been noted in the literature [14,17-25]. Most of these occurred in agricultural sprayers, although some involved manufacturing workers. The signs and symptoms of intoxication were primarily related to the ability of DNOC to increase the metabolic rate. These included profuse sweating, thirst, a feeling of great heat, headache, fatigue, and an increased BMR. In addition, DNOC affected the nervous systems of a number of people, producing numbness in the limbs.

Studies of workers who were exposed to DNOC [17,19-23,25-27] have also examined the fate of DNOC in the blood and the association between blood DNOC levels and the severity of intoxication.

A case of industrial poisoning by DNOC occurred in the United States in a man involved in its manufacture [18]. The episode occurred in the early part of 1943, but the duration of exposure was not stated. The man was hospitalized with signs and symptoms that included a temperature of 102 F, a BMR greater than 400%, rapid pulse and respiration, profuse sweating, shortness of breath, and a cough. The man's palms and soles were stained yellow and it was reported that he had recently lost 20 pounds. He was treated successfully and recovered fully. It was determined that the level of airborne DNOC dust in the workplace was 4.7 mg/cu m. The methods used for sampling and analysis of DNOC were not reported.

In 1952, Bidstrup et al [17] published the details of a survey conducted to determine whether there was a correlation between blood DNOC levels and the onset of toxic symptoms. They collected blood samples from 195 individuals: 23 process workers involved in the manufacture of DNOC for 6 weeks to 5 years, 39 men who used DNOC as a winter wash spray on

fruit trees, 8 of whom had been spraying for more than 50 days, and 133 men who sprayed DNOC on cereal crops for 6 weeks during the summer. Of the cereal crop sprayers, 45 had a blood DNOC level above 10 μg/g, while only 1 process worker and none of the winter wash sprayers had blood DNOC levels that high.

Bidstrup et al [17] suggested that the process workers had lower blood DNOC levels than cereal crop sprayers because there was greater use of protective measures (not specified) in the factory. Only small quantities of DNOC were believed to have entered the blood through the skin. The authors cited the case of one man who had been involved in the manufacture of DNOC for 5 years. His hands, face, and hair were stained bright yellow, but the concentration of DNOC in his blood was only 7.3 μg/g. However, since no correlation has been established between the quantity of DNOC to which one is exposed and the degree of skin staining, the amount of DNOC with which the man came into contact cannot be estimated.

Winter wash sprayers also had less risk of DNOC intoxication than did cereal crop sprayers [17]. A much weaker solution of DNOC was used during the cold weather, and the method of spraying in winter produced larger droplets, which were less likely to remain airborne.

Of the 133 cereal crop sprayers, 20 had blood DNOC levels of 10-20 μg/g, 16 had 20-30 μg/g, 5 had 30-40 μg/g, and 4 had more than 40 μg/g [17]. The four workers with the highest blood levels of DNOC experienced acute poisoning, and one of these, who had a blood DNOC level of 75 μg/g, died.

Good correlation was found between blood DNOC levels and the development of symptoms in one worker who became seriously ill, as described by Pollard and Filbee [19] in 1951. The 27-year-old man was a member of a spraying team that had been applying DNOC to fruit trees for 5 weeks during May and June 1951 and was primarily responsible for mixing the DNOC solution and refilling the sprayer tanks. He had sprayed for a total of less than 3 hours and later said that he had worn the "regulation" personal protective equipment provided, although he had seldom used a face mask. He developed symptoms of poisoning, including headache and general lassitude, and was admitted to a hospital about 52 hours after he was last exposed to DNOC. His hair, sclera, and skin, especially that on his face, hands, and feet, were stained yellow. Vital signs and body temperature were measured, and biochemical investigations, including blood tests, urinalysis, and measurements of blood and urinary DNOC levels and the BMR, were made several times during the patient's 1-month stay in the hospital. DNOC was measured in the blood and urine almost daily.

On the 1st day of hospitalization, the man's body temperature was 102 F, and his pulse, respiration, and blood pressure were 100/minute, 25/minute, and 115/70, respectively [19]. Blood analysis on the 2nd day showed a hemoglobin concentration that was 80% of normal, normal total white and red cell counts, a low neutrophil count (38%), a high lymphocyte count (56%), and a high urea concentration (60 mg/100 ml). The patient's BMR was 275% of normal on the 3rd day and was still as high as 180% the 2nd week after exposure. By the end of the month, neutrophil and lymphocyte counts and urea level were close to normal. The DNOC concentration in the blood was 60 $\mu$g/g on the 1st day and fell slowly to 4 $\mu$g/g by the end of 1

month. The authors noted that the decreasing blood DNOC level corresponded roughly with the improvement in the patient's clinical condition and with a decrease in his BMR. Urinary urea was high (3.6-4.3 g/100 ml) on the first 3 days of hospitalization, the only days for which this parameter was reported. The daily urine volume was low (400-900 cc) for the first few days but then returned to normal (2,000 cc). DNOC was detected in the urine during the entire month. The excretion rate ranged from 9.5 mg/day on the 2nd day to a high of 22 mg/day on the 4th day, and was 5 mg/day a month after the exposure. An electrocardiogram taken at an unspecified time was normal. The patient's body temperature returned to normal by the 5th day, and his condition was already greatly improved. The authors noted that the most striking findings in the patient were high values for BMR, nitrogen excretion, and blood urea.

Varnai and Kote [20] reported that, in Hungary in 1967, 47 women from a crew of 81 people required hospitalization after working in an onion field sprayed with an aluminum salt of DNOC on the previous day. The workers had been instructed not to eat the onions and to wash their hands before eating, but no protective clothing was supplied. Work began in the morning, and, according to the authors, the first signs of poisoning were evident by 4:00 pm. No specific signs were reported. Work stopped at 6:00 pm, and the ill women were admitted to a hospital. They ranged in age from 15 to 44 years, but most were under 20. Three of the women were pregnant; one was in the 2nd month, one was in the 6th month, and one, who was in the 9th month, gave birth 3 days after the exposure episode. The authors characterized the extent of poisoning as mild, moderate, or severe on the basis of blood levels of DNOC, clinical symptoms, and the results of other

laboratory tests. Specific data from the laboratory tests were not reported. The DNOC concentration in the blood was measured in 45 women, although when the measurements were taken was not specified.

Of the 47 cases, 32 were described as mild, 12 as moderate, and 3 as severe [20]. Effects included liver and kidney damage, loss of weight, unconsciousness, visual disturbance, hemorrhaging, and fever. DNOC blood levels were associated with the severity of intoxication. In the patients considered to be moderately or severely poisoned, blood DNOC levels ranged from 20-55 μg/ml. These women were hospitalized for more than 8 days; one remained for 53 days. In contrast, the women who were mildly affected were released from the hospital by the 8th day. The DNOC levels in their blood were lower and ranged from 7 to 37 μg/ml. When a statistical analysis of the blood DNOC levels was done, it was found that the average blood DNOC level in workers who developed toxic effects (32.5 μg/ml) was significantly greater ($P<0.05$) than in those who exhibited no effects (26.1 μg/ml).

The authors [20] believed that DNOC induced labor in the woman who gave birth to a full-term healthy child 3 days after the exposure, but they gave no evidence to substantiate this. They also reported that the other two pregnant women gave birth to healthy children. Six weeks after the exposure, all of the patients were reexamined and declared healthy. It is assumed this included the woman who was still in the hospital, although no specific mention was made of her condition. Even though the women were declared to be in good health, many complained that they suffered from headaches when they worked in the sun.

In 1960, Van Noort et al [21] recounted five cases of DNOC poisoning in the Netherlands, one having a fatal outcome, that occurred in May and

June of 1954 and 1955. The victims were all men between the ages of 25 and 40 who had been spraying DNOC for a period of up to 4 months. The composition of the sprayed material was not specified. The men were all hospitalized and either had experienced or were still experiencing signs and symptoms of toxicity including profuse sweating, feelings of great discomfort from the heat, labored breathing, restlessness, fatigue, and thirst. It was noticed that their hair, skin (especially of the hands), sclera, and nails were stained yellow. The DNOC level in the serum varied from patient to patient. It was 200, 60, and less than 5 μg/ml in three men on the 1st day of hospitalization, and a fourth man had 10 μg/ml a month after he entered the hospital. The man who had a serum DNOC level of 5 μg/ml was not hospitalized until 3 weeks after exposure had ended. These four recovered from the poisoning, but the fifth man, who the authors stated had inhaled a large quantity of DNOC the day before he was hospitalized, went into a coma and died. His rectal temperature 30 minutes after death was 44.5 C, and the serum DNOC level at this time was 1,000 μg/ml.

Markicevic et al [22], in 1972, discussed the results of an examination of 27 workers exposed to DNOC while they were manufacturing a DNOC paste in Yugoslavia. The workers, all men aged 22-48 years (average 31 years), had been exposed to DNOC for 5-30 days prior to the examinations. It could not be ascertained whether exposure to DNOC was by inhalation, skin contact, or both. Eight men were examined between January and March 1968, 11 were examined in August 1968, and 8 others were examined in both the winter and the summer. Serum and urinary DNOC levels, BMR, erythrocyte sedimentation rate, pulse rate, blood pressure, and respiration

rate were measured. The DNOC concentrations in the serum and urine were measured 24 hours after DNOC was last handled. The physical appearance of the workers and their symptoms were also recorded.

The examination results indicated that 11 workers had no signs or symptoms of poisoning [22]. Sixteen others had yellow staining of the hair, nails, hands, and forearms. Two of the 16 workers had increased BMR's (+34% and +30%), while 2 others had increases that the authors attributed to the patients' lack of cooperation in taking the measurements. An increased BMR (+48%) was measured in another worker several weeks before he first was examined by Markicevic et al [22], when his BMR was +19%. It was +2% 11 days later.

Pulse, respiration, and erythrocyte sedimentation rates in the 27 workers were within normal ranges [22]. The serum DNOC levels ranged from 1.0 to 8.73 $\mu$g/ml and the concentration of DNOC in the urine ranged from nondetectable to 4.2 $\mu$g/ml. A statistical analysis of serum DNOC levels and skin staining, which was categorized as normal, yellow, or strongly yellow, showed there was a significant correlation ($P<0.05$) between serum levels and the degree of staining. In addition to yellow coloration of certain body tissues in 16 men, 1 of them experienced profuse sweating, nervousness, palpitations of the heart, and weight loss (6 kg in 1 month), 1 worker sweated excessively and complained of thirst, 1 had frequent diarrhea, and 1 had a blood pressure of 180/105. One of the workers whose skin was unstained also complained of sweating and had reddened conjunctivae and inflammation of the mucous membranes of the throat.

Burkatskaya [26] analyzed the blood of 20 Soviet workers (sex not specified) who prepared a 1% solution of DNOC for spraying fruit trees.

The length of exposure was not stated. At the time of spraying, the air temperature was 8-16.2 C and the relative humidity was 37-70%. Air samples were taken from the breathing zones of workers preparing the DNOC solution and loading it into sprayers. The methods used for sampling and analyzing DNOC were not described. Burkatskaya reported that the average airborne DNOC concentration was 0.0036 mg/liter (3.6 mg/cu m). In 13 of the workers examined, the DNOC concentration in the blood was 3-5 mg% (30-50 μg/ml), and it ranged from traces to 2 mg% (20 μg/ml) in the other 7. No signs or symptoms of poisoning were described.

Several authors [14,23,24] have described effects of DNOC exposure on the peripheral and central nervous systems, in addition to metabolic effects.

Stott [23], in 1956, detailed the effects on two men of DNOC absorbed through the skin. One, aged 47, had worked for 2 months cleaning the aircraft booms used to spray a 20% solution of DNOC in oil. He wore no protective equipment. The other, aged 24, cleaned and serviced aircraft spray systems in which a 20% solution of DNOC in oil was used. He worked for 10 days in the field and 1 week at the home base. The only protective clothing he wore was overalls. Each man said that he washed before eating and did not smoke. Since neither man worked near the actual spraying operation and both denied blowing into the spray jets to clean them, Stott concluded that the major route of exposure was skin contact.

The older man began to notice symptoms about 1 month after his first contact with DNOC [23]. Initially, he felt a prickling sensation on the back of his hands and fingers, which later spread to the legs. He also was sweating excessively on the lower parts of his arms and legs. When he

entered the hospital 3 days after his exposure to DNOC ended, he mentioned that he had been unusually thirsty during the exposure period but that his appetite was unaffected. A medical examination was performed, which included testing for sensation in his limbs, determining DNOC levels in the serum, and measuring his BMR. His palms and soles were stained yellow, his body temperature was 37.3 C, and his pulse rate was 80/minute. He was sweating heavily on the lower parts of his arms and legs, on the backs of his hands, and on his feet, and he felt no sensation from pinprick or cotton wool on the top of his fingers and toes. Depression of the right knee-jerk reflex was the only other indication of abnormality in the nervous system. The serum DNOC level was 7.6 μg/ml 1 week after the last exposure, and the BMR was +6% after 2 weeks. Values for these two indices immediately after the exposure were not reported. The man's condition improved rapidly, and he showed no signs or symptoms of intoxication after 9 days in the hospital.

The second man came to the hospital immediately after his exposure to DNOC ended [23]. He complained that he had had a tingling sensation on the backs of his fingers for the past 4 days and that his legs were numb at night. The man thought that he had lost some weight but did not experience excessive sweating or thirst. A medical examination was performed to test for neurologic disorders. No loss of sensation to pinprick or cotton wool on his hands or feet was detected, and no other effects on the nervous system were evident. His hands were stained yellow, and there was a petechial rash over his left shoulder. His serum DNOC levels measured 1 week after exposure began and on the last day of exposure were 16.8 μg/ml and 11.5 μg/ml, respectively. The patient was free of all symptoms within

1 week after exposure had ended. Stott considered the peripheral neuritis observed in both patients to be the result of local action by DNOC where it contacted the skin rather than a generalized systemic effect of DNOC after it had been absorbed into the bloodstream.

Buzzo and Guatelli [24] published a report in 1949 of two deaths in Argentina caused by DNOC exposure. Three brothers, aged 17, 21, and 21 years, had sprayed a powdered material that contained 10% DNOC for 2 consecutive days when there was a strong wind, an ambient temperature of 38 C, and a relative humidity of 70%. The personal hygiene of the men, as reported by the surviving brother, was poor. They did not change their underwear or wash before continuing work on the 2nd day. In the late afternoon of the 2nd day, two of the men complained of discomfort, thirst, and excessive sweating, and one of them was unable to walk without assistance. The three men were admitted to a nearby clinic. They had previously been in good health, and they had no history of smoking or drinking.

One of the 21-year-olds and the 17-year-old died shortly after they entered the clinic [24]. Each had exhibited identical signs and symptoms, including profuse sweating, labored breathing, hyperthermia, tachycardia, intense thirst, yellow staining of the skin, a sensation of feeling hot, and mental confusion. Muscular rigidity developed shortly before they died. Autopsies were performed 8 days later. The skin bore blisters filled with a dark red liquid, and the epidermis was edematous. Internal examinations of both corpses revealed dark-gray, friable, enlarged livers, dilated intestinal loops, darkly colored, friable lungs, and slate-colored spleens. The surviving brother was thirsty and perspiring when he entered

the clinic, and his skin was stained yellow. He returned home the same day, but his condition worsened. He lost the motor function of his legs, was dyspneic, exhibited signs of confusion, and sweated profusely. His body temperature was 39 C. He was readmitted to a hospital, and his condition improved gradually. He was released on the 8th day after the initial exposure had taken place.

Sovljanski et al [14], in 1971, described two cases of lethal intoxication from DNOC that occurred in Yugoslavia. Both involved farmers, aged 50-60 years, who were exposed while spraying fruit trees with DNOC. They used no personal protective equipment. One man's hands and clothes became yellow. After the day's work, he washed and went to sleep, but during the night he became comatose and was taken to the hospital the next morning. His pulse rate (126/minute) and blood pressure (170/95) were both elevated. The farmer's condition improved with treatment, and he was removed from intensive care after 7 days. There were still some signs of intoxication, however, including slow pupil response, increased tendon reflexes, and slightly excessive muscle tone. He was discharged from the hospital but died 3 days later. Death was attributed to choking on food eaten during breakfast.

In the second case recounted by Sovljanski et al [14], the circumstances were similar to those of the first, and death was also said to have resulted from choking on food. The authors thought that DNOC indirectly caused these deaths by impairing swallowing. This belief was not substantiated by any direct evidence, but microscopic examination of the brains after death showed that they had been affected. There were

signs of hemorrhage and infarction of the brain, areas of demyelination, and hyaline thrombi. The cells of the reticular formation showed chromatolysis. There was cytolysis of Purkinje cells and karyolysis of most brain cells.

Some authors have investigated the effectiveness of personal protective equipment in reducing exposure to DNOC. Burkatskaya [25], in conjunction with a study on the effects of airborne DNOC on cats (see Animal Toxicity section), examined the working conditions present in the manufacture and application of DNOC in Russia. He measured the concentrations of DNOC in the breathing zones of workers but did not describe the methods of sampling and analysis. Nonspecific effects on the workers were recorded. Workers exposed to DNOC at concentrations ranging from 0.0003 to 0.0029 mg/liter (average, 0.0009 mg/liter or 0.9 mg/cu m) displayed changes in the cardiovascular system, in the central and autonomic nervous systems, in the gastrointestinal tract, and in the cell pattern of the peripheral blood. The author did not describe the changes in detail. When DNOC was used agriculturally, its concentration in the air ranged from 0 to 0.013 mg/liter (average, 0.0007 mg/liter or 0.7 mg/cu m). Slight changes in the blood and autonomic nervous system were reported, but there were only isolated unspecified complaints from the workers. Since the author did not specify the changes that were observed, their magnitude and importance cannot be ascertained.

Van Noort et al [21] investigated the effectiveness of the personal protective equipment used by eight sprayers in May 1956. The authors measured the serum DNOC levels and recorded the quantity of DNOC used (expressed as the weight of DNOC) during the course of a 1-month spraying

period. From this study, they presented the results found in four workers. In one sprayer, who wore no protective devices, the serum DNOC level rose continuously during the spraying period, increasing at a rapid rate after the 1st week of exposure. By the end of 1 month, when he had sprayed over 800 kg of DNOC, his serum DNOC level was 64 μg/ml. A second worker wore gloves and a fresh-air hood during the spraying operation. Although he had sprayed 480.6 kg of DNOC in 23 days, his serum DNOC level reached no more than 16 μg/ml, indicating that the protective equipment offered protection but did not totally prevent contact with DNOC. Some of the workers who wore a fresh-air hood but no gloves absorbed little DNOC; others received an appreciable amount of the compound. In two of the sprayers from the latter group, the serum DNOC levels after 1 month were 65 μg/ml and 61 μg/ml. Each man had sprayed a total of 649 kg of the DNOC formulation. The authors did not report whether any signs or symptoms of intoxication had developed in the workers.

In May 1958, Van Noort et al [21] studied 24 sprayers to further examine the effectiveness of personal protective devices in preventing exposure to DNOC. Serum DNOC levels and the quantity of DNOC used were determined during a 3-week spraying period. The results from three workers were presented. In one worker who used no protective equipment, the serum DNOC level rose continuously during the spraying period, and by the end, after about 700 kg of DNOC had been sprayed, it was 75 μg/ml. Another sprayer, who wore both gloves and a plastic mask that he changed daily, had used a total of 650 kg of DNOC, but his serum DNOC level never rose above 10 μg/ml. A third worker, who used gloves carelessly and did not wear a mask, absorbed an appreciable amount of DNOC. By the end of the spraying

period, he had used about 450 kg of DNOC, and his DNOC serum level reached 65 μg/ml. In most of the sprayers there was an unexplained sudden rise in serum DNOC levels in the last days of the spraying period. The environmental temperature rose about 8 C in the last few days but the authors could not decide whether this was related to the increased serum DNOC levels.

Van Noort et al [21] also measured the serum DNOC levels in 10 of the 24 sprayers weekly for 2 months after the spraying period ended. They found that DNOC was eliminated from the serum slowly and that the rate varied from individual to individual. On the last day of the spraying period, serum DNOC levels ranged from 11 to 88 μg/ml, and 2-8 weeks elapsed before for DNOC was cleared from the serum. The amount of time needed for DNOC to be totally eliminated from the serum was directly related to the quantity of DNOC in the serum on the last day of the exposure period.

The findings by Van Noort et al [21] show that both inhalation of and dermal contact with DNOC can lead to appreciable absorption into the blood stream. A worker who wore a hood but no gloves and workers who wore gloves but no respiratory protection had serum DNOC levels of 61-65 μg/ml. In contrast, the use of equipment to protect against inhalation and dermal contact prevented appreciable accumulation of DNOC in the serum.

Batchelor and coworkers [27] attempted to ascertain the quantities of DNOC to which a group of spray operators, who used DNOC as a blossom-thinning agent, were exposed. The sprayed material was a slurry containing 19% of the sodium salt of DNOC, 5% sodium butyl naphthalenesulfonate, 2% sodium chromate, and small amounts of sodium chloride and sodium sulfate, which was then diluted with water to 0.02-0.08% DNOC. Spraying was done

during April and May when the temperature ranged from an average low of 37 F to an average high of 66 F. The workers were generally exposed for no more than 5 days, 6 hours/day. Dermal exposure was estimated from the amount of DNOC collected on absorbent pads placed on the forearms, shoulders, thighs, and the back and front of the necks of the spray operators. Some workers also wore respirators with collection filters so that respiratory exposures could be measured. Urine and plasma samples were taken from several workers to determine the concentrations of DNOC. Urinary DNOC levels were measured before, during, and after exposure, while plasma DNOC levels were checked within 24 hours and 7 and 11 days after the last exposure to DNOC. Plasma DNOC levels were measured in six workers exposed to DNOC for periods ranging from 5 to 48 hours.

The authors [27] found from examination of 300 pads that a worker was dermally exposed to an average of 63.2 mg of DNOC/hour, assuming that DNOC did not penetrate the clothing. The average respiratory exposure, calculated from 74 samples, was 0.4 mg of DNOC/hour. (Assuming that a worker inhales 28.6 liters of air/minute, which is a suggested minute volume for a 68.5 kg man doing light work [28], this corresponds to an airborne DNOC level of 0.23 mg/cu m.) Only small amounts of DNOC were detected in the urine. Of 183 samples tested, only 5 had DNOC levels greater than 0.5 ppm; these ranged from 0.6 to 1.3 ppm. Plasma DNOC levels were also low. One day after exposure ended, the plasma levels ranged from 1.4 to 4.0 ppm (approximately 1.4-4.0 μg/ml). After 7 days, the levels ranged from 1.6 to 4.3 ppm (1.6-4.3 μg/ml), and, by 11 days, they ranged from less than 1.0 to 2.7 ppm (1.0-2.7 μg/ml). The authors reported that workers showed no symptoms of intoxication.

## Epidemiologic Studies

No reports of epidemiologic studies of persons exposed to DNOC were found in the literature.

## Animal Toxicity

Animal studies have investigated the absorption of DNOC through the respiratory system [29,25,30], skin [15,26,31], and gastrointestinal tract [15,26,29,31,32] and the resulting blood levels and systemic effects. Authors have expressed blood DNOC values either as weight of DNOC/volume of serum or weight of DNOC/weight of whole blood. Parker et al [33] observed that over 90% of the DNOC detected in the blood was in the plasma and only small amounts were in the red blood cells. Because of this fact, numerically similar DNOC whole blood and serum values do not represent equivalent DNOC concentrations and should not be compared quantitatively. (In the following reports, the age, sex, and number of animals used in the experiments will be given if known).

(a) Inhalation

King and Harvey [29] exposed rats to a sublimate of DNOC, which acted as an aerosol. DNOC aerosol was generated by passing air at the rate of 1 liter/minute over an apparatus in which DNOC was heated, and 0.2 mg of sublimate was produced per hour. The aerosol generator and the cage containing the rats were enclosed in a glass chamber through which the airflow could be regulated and from which the outflow could be sampled for DNOC analysis.

In one experiment, four rats were exposed to DNOC aerosol at a

reported concentration of 0.1 mg/cu m for 5 hours [29]. The rats were removed at hourly intervals during the exposure, and blood samples were taken from the tail vein to measure DNOC levels. The rats were killed immediately after the exposure period, and DNOC was measured in the lungs and in the alimentary canal and its contents. The blood DNOC levels gradually rose during the exposure from about 20 μg/g after 1 hour to about 50 μg/g by the 5th hour. (These blood DNOC levels bring into question the reported airborne DNOC concentration. Even if one assumes that at a concentration of 0.1 mg/cu m all of the DNOC that was inhaled remained in the blood DNOC, a blood DNOC level of 20 μg/g could never be attained in 1 hour. In addition, the blood levels attained after exposure at 0.1 mg/cu m were similar to those attained at 100 mg/cu m, which is not likely, given the large difference in exposure concentrations.) The lungs of four rats contained 16, 20, 31, and 28 μg of DNOC/g, and the corresponding concentrations in the alimentary canal and contents were 2.5, 3.1, 2.8, and 2.2 μg of DNOC/g. These data suggested to the authors that the blood DNOC levels resulted mainly from inhalation of the aerosol and not from exposure by other routes. If there had been an appreciable amount of ingestion of contaminated food or water by the rats, DNOC levels in the alimentary canal would have probably been higher.

In a second inhalation experiment described by King and Harvey [29], five rats were exposed to DNOC aerosol at a concentration of 100 mg/cu m for 4 hours in a chamber maintained at 28-30 C. Respiratory rate, body temperature, and blood DNOC levels were measured hourly during the exposure period and again 20 hours after the exposure ended. The rats were kept at 20-22 C after they were removed from the chamber. In all five rats, blood

DNOC levels generally rose over the 4 hours, reaching a peak of between 16 and 64 μg/g in the 4th hour. Body temperatures decreased in the 1st hour in three rats and by the 4th hour it was lower than the preexposure level in three and was higher than the preexposure level in the other two animals. Respiratory rates varied during the 4 hours, but they were lower than the initial values in four of the five rats by the end of the period. In four rats, the blood DNOC levels were lower at 20 hours than they were immediately after exposure. Twenty hours after exposure, the blood concentrations of DNOC were between 17 and 29 μg/g in the five rats. The respiration rates had increased appreciably in three of the rats, and body temperatures had increased in two. The authors suggested that, although the compound was not accumulating in the blood after exposure ended, there might be an accumulation of the metabolic effects of DNOC, as indicated by delayed changes in respiration rates and body temperatures. However, the data were not conclusive since the results were so different in the five rats.

Burkatskaya [25] also examined the effects of DNOC inhalation by exposing 36 cats to either a liquid (fine dispersion of solution) or a solid (dispersion of solid) aerosol of DNOC in chambers that permitted exposure of the head only. The methods of generating the aerosols were not given in the report. Groups of three cats each received a single 4-hour exposure to the liquid aerosol at a concentration of 0.0004, 0.0014, or 0.04 mg/liter (0.4, 1.4, and 40 mg/cu m, respectively) or to the solid aerosol at a concentration of 0.036 or 0.06 mg/liter (36 and 60 mg/cu m). Six cats each received a single 4-hour exposure to the liquid or solid aerosol at a concentration of 0.1 mg/liter (100 mg/cu m). Three cats were

exposed for 4 hours daily for 1 month to the solid aerosol at 0.002 mg/liter (2 mg/cu m), and three cats each were exposed daily for 4 hours to the liquid aerosol at 0.0002 mg/liter (0.2 mg/cu m) for 2 or 3 months. Toxic effects were judged by changes in body weight, appetite, body temperature, cell counts, blood catalase and peroxidase activities, blood sugar levels, and erythrocyte sedimentation rate (ESR). The DNOC content of the blood or serum was also determined. In cats that showed toxic effects, measurements were made at unspecified intervals for up to 2 weeks after exposure ended. The author did not mention using controls in the experiment. Presumably, results obtained during the treatment periods were compared to preexposure values. It was not indicated whether measurements were made during the 1-month exposure or only after the exposure ended, but they were taken during the course of the 2- and 3-month experiments.

No deaths occurred in cats exposed to the liquid aerosol at a DNOC concentration of 1.4 mg/cu m or less or to the solid aerosol at 60 mg/cu m or less [25]. One cat exposed to the liquid aerosol at 40 mg/cu m and two cats exposed to the liquid aerosol at 100 mg/cu m died. The author noted that animals surviving the exposure at 40 mg/cu m exhibited increased body temperature, leukocyte count, and blood sugar concentration and decreased hemoglobin concentration, erythrocyte count, and catalase and peroxidase activities. Effects from a single 4-hour exposure to the liquid aerosol at 100 mg/cu m were variable. Catalase activity increased in three cats but decreased in the three others. Blood sugar concentration rose in four cats but remained unchanged in two. Peroxidase activity decreased in all six, while body temperature rose in only three. In cats exposed once to the solid aerosol of DNOC at 36 or 60 mg/cu m, some toxic signs were observed,

including salivation, lacrimation, spasms in the eyelids, sneezing, mucous nasal secretion, labored breathing, and sluggishness. Two cats also exhibited twitching, tremors, and ataxia. Hemoglobin concentrations and erythrocyte counts were decreased, while blood sugar was increased 20-25%. The ESR increased by 8-37 mm/hour. There were also slight decreases in peroxidase and catalase activities. Effects from exposure to the solid aerosol at 100 mg/cu m were similar in nature but more pronounced. Two of six cats exposed at this concentration died.

Blood and serum DNOC levels varied in the cats [25]. In cats that inhaled the liquid aerosol, blood DNOC levels were 2 mg% (20 μg/ml) in one on the 2nd day after exposure to 0.4 mg/cu m and 4 mg% (40 μg/ml) in the one that died after exposure at 40 mg/cu m. The DNOC serum level was 6-15 mg% (60-150 μg/ml) in those cats exposed to 100 mg/cu m. Blood DNOC levels of up to 10-15 mg% (100-150 μg/ml) were detected for 2 days after exposure to the solid aerosol at 36, 60, or 100 mg/cu m. DNOC was eliminated from the blood of all cats within 8 days of exposure.

A daily 4-hour exposure to DNOC at 2 mg/cu m for 1 month resulted in the deaths of two of three cats [25]. One died on the 26th day and one died 6 days after the exposure ended. Other changes noted were similar to those seen in cats exposed once to the solid aerosol. DNOC was not detected in the blood of these cats.

Cats exposed daily for 2 or 3 months to DNOC at a concentration of 0.2 mg/cu m had only slight increases in body temperature, leukocyte count, and ESR and slight decreases in hemoglobin concentration, erythrocyte count, and catalase and peroxidase activities [25]. Changes began to appear 1-2 weeks after exposure began, after which values remained stable.

None of the cats that were exposed at this concentration died. Blood DNOC levels of up to 1-2 mg% (10-20 μg/ml) were detected in two of the cats.

Burkatskaya [25] observed several effects from exposure to DNOC at concentrations as low as 0.2 mg/cu m, including changes in leukocyte and erythrocyte counts and peroxidase and catalase activities. The small number of cats in each exposure group and the absence of data for some of these groups makes the results questionable. However, the absence of these details does not invalidate the general conclusion that chronic exposure (2-3 months) of cats to DNOC at 0.2 mg/cu m produced slight changes in blood counts and enzyme activities.

Popov and colleagues [30] investigated the effects of DNOC administered simultaneously by the oral and the inhalation routes. Three groups of 20 albino rats each were given DNOC perorally (0.005 mg/kg), by inhalation (0.001 mg/cu m), or by combined exposure at 0.005 mg/kg perorally and 0.001 mg/cu m by inhalation. A fourth group of rats was used as controls. The control rats and those given DNOC perorally were kept in exposure chambers supplied with air. The exposure period lasted 2 months and included continuous exposure to DNOC or supplied air by inhalation and, for the appropriate groups, daily peroral administration. Observations and tests were made at 24 hours and 10, 30, and 60 days after the start of the exposure. They included monitoring of the rats' behavior and physical condition and measurements of oxygen consumption, erythrocyte and leukocyte counts, hemoglobin concentration, and the activities of the serum enzymes glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, lactic dehydrogenase, peroxidase, and catalase. The level of DNOC in the blood serum was measured in the middle and at the end of the

experiment. Although no specific data were presented, the authors reported that there were no adverse effects from DNOC at the concentrations administered.

(b) Dermal Exposure

The effects of DNOC applied to the skin of rats and rabbits were examined by Ambrose [15]. DNOC in a 2% aqueous solution (quantity not specified) was applied daily for 30 days to the depilated backs of 10 rats and to the depilated ventral surfaces of 6 rabbits. An unspecified number of rats served as controls. No signs of local irritation or systemic effects were evident in any of the animals given DNOC. The treated rats and the controls gained weight at similar rates.

Ambrose [15] also introduced five drops of a 1% aqueous solution of DNOC into the conjunctival sac of each of six other rabbits every 30 minutes for 6 hours. No signs of irritation were apparent during the 6-hour treatment period or 24 hours later.

The toxicity of DNOC in guinea pigs by dermal application was investigated by Spencer et al [34]. Single doses of 100-1,000 mg/kg of DNOC in an alcoholic solution were applied to the shaved abdomens of 27 guinea pigs. To facilitate absorption, the treated area of the skin was kept wet with ethanol for 4 hours after DNOC was applied. Deaths were recorded until the last surviving guinea pigs recovered fully from intoxication. This was the maximum observation period for recording deaths, provided full recovery could be defined satisfactorily. The authors found 200 mg/kg to be the highest "survival dose," ie, all five guinea pigs given this dose survived. The lowest "lethal dose" was 500 mg/kg; all five guinea pigs given this dose of DNOC died.

Burkatskaya [26] applied DNOC to the skin of rabbits in single doses ranging from 100 to 500 mg/kg in a dry form or as a "thick mush" and in single doses of 500 and 1,000 mg/kg as a 3% aqueous suspension. The procedure used for applying was not described. The concentration of DNOC in the blood was measured in rabbits given the aqueous suspensions of DNOC. DNOC applied in the dry form or as a thick mush produced no local irritation or systemic effects. The 500 mg/kg dose of the aqueous suspension also produced no local irritation, but it did cause changes in respiration, cardiac activity, and temperature regulation. The author did not describe the method used to measure those changes or specifically what was observed. DNOC was detected for 8-12 days at a concentration of 4-8 mg% (40-80 μg/ml) in the blood of the rabbits given 500 mg/kg of DNOC in an aqueous suspension. The 1,000 mg/kg dose of DNOC was reported to be the LD50. One hour after this dose was given, the blood levels were 2-4 mg% (20-40 μg/ml). The blood concentrations reached maximums of 10-40 mg% (100-400 μg/ml) and some of these rabbits died. The author reported finding no direct relationship between blood levels and the development of toxic effects.

Arustamyan [31] described the effects of an aqueous solution of DNOC applied to the skin on the backs of mice for an unspecified time. No mention was made of the use of control mice. The author observed the animals for signs of intoxication, recorded the number of deaths, and examined the internal organs following death.

The LD0 was determined to be 80 mg/kg, and the LD50 was 186.7 mg/kg [31]. Signs of poisoning included severe agitation, muscular twitching, labored breathing, extreme thirst, and loss of appetite. Post-mortem

examination of the mice revealed enlarged livers with spot hemorrhages and necrotic foci, spleens twice the normal size, and pulmonary edema. Cutaneous application of the aqueous suspension of DNOC did not produce skin irritation.

(c) Other Routes of Administration

The acute toxicity of DNOC given by subcutaneous injection has been investigated in a number of studies [15,17,35]. Ambrose [15] reported that the minimum fatal dose of DNOC in male and female rats (100-125 g) was 20 mg/kg. Signs of intoxication included hyperactivity followed by depression, labored breathing, asphyxial convulsions, and coma. Rigor mortis developed immediately after death. Parker et al [33] found that the LD50 of 1% DNOC in a weak sodium carbonate solution was 24.6 mg/kg in rats and 24.2 mg/kg in mice. Intoxicated animals exhibited increased respiratory rate and prostration. Rigor mortis was apparent immediately after death. Harvey [35] found that the LD50 values in albino rats for pure DNOC and for four commercial samples of DNOC were 25.6 and 26.2-27.5 mg/kg, respectively. The samples were prepared as 1% (w/v) saline solutions. In hooded rats, the LD50 values were 28.5, 27.5-30.0, and 36.5-39.1 mg/kg for pure DNOC, a commercial preparation, and the diethylamine salt of DNOC, respectively [35].

Some investigators have studied the toxicity of DNOC administered by stomach tube [15,26,31,32,34]. According to Ambrose [15], the minimum fatal dose of DNOC for 150 g male rats was 30 mg/kg. Signs of intoxication were similar to those observed in rats given DNOC by subcutaneous injection. Burkatskaya [26] reported that the LD50 values in mice, rats, and cats were 47, 85, and 50 mg/kg, respectively. Signs of intoxication

observed in the cats included accelerated breathing, salivation, sluggishness, muscular twitching, and loss of appetite. Arustamyan [31] determined that the single dose oral LD50 in mice was 16.4 mg/kg. Signs of intoxication included severe agitation, muscular twitching, thirst, and refusal of food. Post-mortem examination revealed enlarged livers and spleens and inflammation of the intestinal mucosa. The single dose oral LD50 values for DNOC, given as a 35% solution of its ammonium salt, were 8.4, 8.3, and 24.8 mg/kg for pheasants, partridges, and hares, respectively [32]. Poisoned animals exhibited heavy breathing, asphyxial spasms, and muscular rigidity. Edema and emphysema of the lungs, dilation of the heart, inflammation of the mucous membranes of the intestines, and changes in kidney cell morphology were found in animals that died. Spencer et al [34] examined the effects of DNOC given in olive oil to 100 white rats of both sexes by stomach tube. The largest single dose survived by all rats so treated was 10 mg/kg, while 50 mg/kg was the smallest dose that produced 100% mortality. The authors attributed death to the pyretic effect of DNOC.

The distribution of DNOC in the body tissues and its cumulative properties have been studied using the subcutaneous, intraperitoneal, and oral routes of administration [15,29,32,33]. Ambrose [15] gave 20 rats, weighing about 100 g each, daily subcutaneous injections of 15 mg/kg of DNOC for 30 days. Controls were used, but the author did not describe the experimental conditions for this group. The urine was examined at unspecified intervals for glucose, albumin, and red cells. Hemoglobin concentrations and red blood cell counts were determined at the start of the experiment and on the day after the last injection. After 30 days, the

rats were killed, and portions of the urinary bladder, stomach, small intestine, kidneys, liver, spleen, heart, and lungs were examined microscopically. No toxic signs developed in the animals given DNOC, and the urinary and blood findings were no different from those of the controls. Rats given DNOC had a slightly larger mean increase in body weight (46%) than the controls (42%) during the 30-day period. No changes were observed in those tissues examined microscopically. The author concluded that daily sublethal doses of DNOC did not accumulate in rats.

Parker et al [33] observed the effects on rats and rabbits of 5 mg/kg doses of DNOC injected subcutaneously at 1-hour intervals. The DNOC was given as a 1% solution in weak sodium carbonate solution. A single 5 mg/kg dose produced no signs of poisoning in either rats or rabbits; however, some animals died after the fifth to seventh injections. Each animal received a total of 25-35 mg/kg, an amount similar to the LD50 for a single subcutaneous injection. This indicated to the authors that DNOC accumulated in the animals, but the total dose was given over only 5-7 hours. The authors also gave dogs subcutaneous injections of 5 or 10 mg/kg of DNOC daily for 12 consecutive days. They stated that there was no evidence of an accumulation of toxic effects from repeated doses of DNOC.

King and Harvey [29] investigated the cumulative properties of DNOC given in repeated daily doses to rats weighing 104-253 g and to rabbits weighing 1,400-1,805 g. DNOC was given by stomach tube for 8 consecutive days to six female rabbits at 25 mg/kg/day, to six female rats at 20 mg/kg/day, to six male rats at 10 mg/kg/day, and to five male rats at 5 mg/kg/day. DNOC was also administered by daily intraperitoneal (ip) injection for 14 days to three male and three female rats at 10 mg/kg/day

and to three male and three female rats at 5 mg/kg/day. The blood concentration of DNOC was measured 24 hours after each dose was given.

After the second daily dose of DNOC was given to the rats by either route, the blood concentration of DNOC was significantly higher than it was after the first dose [29]. Succeeding ip doses did not produce blood levels higher than those observed after the second dose. However, succeeding doses of 5 and 10 mg/kg by stomach tube caused small increases in the blood levels from the 3rd day onward, while the 20 mg/kg dose produced results similar to those caused by the ip injections. The authors did not speculate about these differences in the rats being related to the sex differences in the dose groups. In the rabbits, the DNOC level in the blood was no greater after the second dose than after the first.

Janda [32] gave pheasants and partridges three daily doses of DNOC by stomach tube as a 35% solution of the ammonium salt. The LD50 values, expressed in terms of the daily dose, were 7.1 mg/kg/day and 11.1 mg/kg/day for the pheasant and partridge, respectively. These LD50's were similar to those reported by Janda for a single dose oral LD50 of DNOC (8.4 and 8.3 mg/kg) and suggest that DNOC is eliminated rapidly from the pheasant and partridge.

Parker et al [33] found that DNOC injected subcutaneously disappeared from the blood at various rates in different species. Single 10 mg/kg doses of DNOC were administered subcutaneously to an unspecified number of dogs, cats, rabbits, and rats. Serum concentrations of DNOC were measured daily for 6 days after the injection. Other rats, rabbits, and dogs were given daily 10 mg/kg doses of DNOC, and the concentration of DNOC in the serum was measured 24 hours after each injection. The rats were given two

injections, and the rabbits and dogs were each given five. DNOC given in one injection was completely eliminated from the serum of rabbits within 24 hours, while blood DNOC levels were between 30 and 40 μg/ml in the rats, cats, and dogs at this time. It took 4 days for DNOC levels to fall to zero in rats and cats, and 6 days in dogs. The authors reported that serum levels of DNOC were no higher on succeeding days in rats, rabbits, and dogs that received daily doses than they were 24 hours after the first dose. However, that statement contradicted the data presented for the dogs, which showed that the serum DNOC level rose from about 45 μg/ml 24 hours after the first dose to 60 μg/ml after the second dose and peaked at 67 μg/ml after the third dose. The DNOC concentration then began to fall, although two additional doses were given to the dogs. Six days after the fifth dose, the concentration was about 10 μg/ml.

The distribution of DNOC was measured in various tissues in animals given either single or repeated injections of DNOC. In one experiment, Parker et al [33] gave rats 1.5 mg of DNOC by subcutaneous injection, and one or more were killed 0.5, 1, 2, 3, 4, 5, and 6 hours after the dose was administered. Most of the DNOC that was recovered in the rats appeared in the serum. In the one rat killed 30 minutes after being given 1.5 mg of DNOC, 0.725 mg was recovered; 83% of this was found in the serum. From rats killed 6 hours after the injection, an average of 0.37 mg of DNOC was recovered; 72% of this was in the serum. Small amounts of DNOC were also found in the heart, lungs, kidneys, liver, and spleen.

In another experiment, the authors [33] gave single subcutaneous injections of 20 mg/kg of DNOC to 19 rats and 40 daily injections of the same dose to 9 rats. They found that the mean DNOC concentration in the

serum of the rats 24 hours after the single injection was 45±1.6 μg/g, which was similar to that measured 24 hours after the last of 40 injections. A similar pattern was observed in the liver and kidneys, although the mean DNOC concentrations in these organs were much smaller than that found in the serum.

These authors [33] also measured the excretion of DNOC in the urine of dogs and rabbits given single or repeated subcutaneous injections of DNOC. The total quantity that was administered ranged from 0.5 to 80 mg. Urine was collected during the time injections were being given and for 3 days after the last injection. Between 4 and 10% of the total amount of DNOC injected was recovered in the urine as DNOC, and there was no difference in the percentage recovered from rabbits and from dogs.

King and Harvey [29] measured blood levels of DNOC in rats and rabbits that were exposed to DNOC by various routes of administration. They gave each of 12 albino rats a single 30 mg/kg dose of DNOC in 0.9% saline by stomach tube and then measured the distribution of the compound in the rats' bodies. Two rats were killed at each of the following intervals: 1, 2, 4, 7, 24, and 48 hours after the dose. The blood, stomach, small intestine, large intestine, and contents of the alimentary canal were analyzed for DNOC. An average of 19% of the dose was recovered in these tissues 1 hour after the exposure; 12% was recovered after 2 hours, and 3% after 7 hours. By 48 hours, only the large intestine and the alimentary canal contents contained appreciable amounts of DNOC. Blood DNOC levels reached a peak of about 50 μg/g between 2 and 7 hours after the single dose was given.

An additional 17 rats were given DNOC by stomach tube in single doses of 5, 10, 20, 40, 50, or 100 mg/kg [29]. Twelve rats were given the 40 mg/kg dose, and one rat each received the other doses. Samples of blood were taken from tail veins, and DNOC was measured at various intervals for up to 24 hours after the doses were given. One rabbit was given a single 10 mg/kg dose by stomach tube and a second was given 20 mg/kg. Blood samples were taken from their ears 2, 4, 6, 8, 12, and 24 hours later, and blood DNOC levels were measured. In both the rats and the rabbits, DNOC concentrations in the blood peaked within 8 hours; however, by 24 hours the levels were much lower in the rabbits than in the rats. Twenty-four hours after the 10 mg/kg dose was given, the blood levels were 25 μg/g in the rat and 4 μg/g in the rabbit. The blood level was 2.5 μg/g in the rabbit given 20 mg/kg. The rat that received this dose died before the 24-hour measurement could be made, but, even in the rat given 5 mg/kg, the blood DNOC level was higher than in the rabbits given 10 or 20 mg/kg. It was 12 μg/g after 24 hours. Maximum blood levels of 101, 92, and 88 μg/g were attained after administration of the 40, 50 and 100 mg/kg doses, respectively.

Four rats were each given one ip injection of DNOC at doses of 1, 5, 10, or 20 mg/kg [29]. Blood levels of DNOC were measured 1, 3, 5, 8, 11, and 27 hours after the doses were given. The injections generally produced higher blood concentrations of DNOC that peaked at a faster rate than did similar doses given to rats by stomach tube. This was especially evident at a dose of 20 mg/kg.

Several studies have been conducted to investigate the effect of environmental temperature on the toxicity of DNOC [29,33,36]. The

experimenters have given DNOC by various routes of exposure to several different animal species.

The effects of environmental temperature on the toxicity of DNOC and on the accumulation of DNOC in the blood were studied in rats by King and Harvey [29]. Groups of 24 rats each were given DNOC in single doses ranging from 5 to 50 mg/kg by stomach tube; 12 rats at each dose were kept at 20-22 C and 12 at 37-40 C. After receiving a 20 mg/kg dose, all of the rats at 20 C, but only half of those at 37 C, survived. Of the rats given 40 mg/kg, 16% of those kept at 20 C and all of those kept at 37 C died. At 50 mg/kg, 33 and 100% of the rats kept at 20 C and 37 C, respectively, died. An analysis of the data indicates that the approximate LD50 values for rats kept at 20-22 C and 37-40 C were 55 and 20 mg/kg, respectively. The authors also reported that blood DNOC levels did not differ in groups of hooded rats kept at different environmental temperatures following a single oral dose of 40 mg/kg.

King and Harvey [29] obtained inconsistent results in their studies of the effects of environmental temperature on blood DNOC levels in rabbits given DNOC dermally. In one experiment, blood DNOC levels were no different in two groups of rabbits kept at different temperatures. However, in another experiment, the authors found that blood DNOC levels rose after a group of rabbits was moved to a warm room.

Other investigators have observed increases in the toxicity of DNOC with increasing environmental temperatures. The LD50 for a single subcutaneous injection of DNOC was lower in rats kept at 36-37 C than in rats at 5-10 C [33]. Mice given a subcutaneous injection of DNOC and kept at 40 C died in a shorter time than those kept at 10 or 20 C [36].

Vashakidze [37] investigated the effect of DNOC administration on the reproductive cycle of rats. In one experiment, female rats (weight and number unspecified) were given DNOC by mouth repeatedly for 6 months (exact regimen not reported) in doses of 2, 5, or 10 mg/kg. At the end of 6 months, hypophyseal suspensions of unspecified concentration were prepared from these rats and administered by an unstated route to immature female rats weighing 15-20 g. One control group of immature female rats received hypophyseal suspensions from untreated donor rats, and a second control group of immature female rats received no suspension. The gonadotropic activity of the hypophyses of DNOC-treated rats was measured by monitoring the development of the sexual organs in the recipient rats. Toxic effects on the donor rats were also monitored.

Donor rats that received 10 mg/kg of DNOC exhibited a 10-18% lag in weight gain, fatty degeneration of some organs, various disorders in the functioning of the reproductive glands, and a reduction in the number of phases of heat [37]. The 2 and 5 mg/kg doses did not produce this spectrum of toxic effects, although the 5 mg/kg dose had an unspecified effect on the reproductive glands. When immature rats were given hypophyseal suspensions from rats treated with repeated 10 mg/kg doses of DNOC, the average weights of the uteri and ovaries of the recipient rats were 38 and 36% greater, respectively, than those of the rats that were given hypophyseal suspensions from untreated donors. This demonstrated an increased activity of gonadotropin in the pituitaries of rats treated with 10 mg/kg of DNOC. Hypophyseal suspensions from rats given the 2 and 5 mg/kg doses produced slight or no change in the weights of the ovaries or

uteri of the immature rats. Results from the second control group were not reported.

In a second experiment, Vashakidze [37] studied the reactivity of the vaginal mucosa in rats following poisoning with DNOC. The protocol of this experiment is unclear. Apparently, immature female rats were treated with DNOC in doses of 2, 5, or 10 mg/kg for 6 months. At the end of this time, they were then treated for 5 days with 5,000 units of folliculin (estrogen). A second group of immature rats received no DNOC but were given the same amount of folliculin 1 month after having their ovaries removed. Control rats, either given DNOC or ovariectomized, received injections of olive oil instead of folliculin. Vashakidze reported that a dose of 10 mg/kg of DNOC disrupted the reactivity of the vaginal mucosa to folliculin in about 10% of the rats, as determined by vaginal smears. At lower doses, no disruption was seen. Results for the ovariectomized animals were not reported.

In a third experiment, Vashakidze [37] gave an unstated number of female rats DNOC repeatedly for 6 months in doses of 2, 5, or 10 mg/kg, which produced disruption of the estrous cycle. These rats were then given transplanted ovaries from untreated 3-week-old rats. Transplants were also given to rats that had been surgically ovariectomized. Transplanting of ovaries to rats that had been given DNOC resulted in restoration of the estrous cycle in 70-90% of the rats within 20 days. Transplantation of ovaries also restored the appearance of the body and horns of the uterus, which had atrophied following DNOC poisoning. When the transplanted ovaries were removed, cycling stopped in most animals (number unspecified). Where cycling continued, the author attributed this to a restoration in the

functioning of the animals' own ovaries and to a residual influence of the transplants. In ovariectomized animals, transplantation of ovaries restored cycling within 20-40 days. The number of rats that continued to cycle, however, decreased in the next few months because the ovaries were resorbed. Vashakidze [37] concluded, particularly from the data of the third experiment, that DNOC disrupted the reproductive cycle by direct action on the ovaries. However, because of the experimental design and because the data were not clearly presented, it is difficult to substantiate this conclusion.

Kreczko et al [38] studied the effect of DNOC on glycoprotein biosynthesis in guinea pigs. Thirty male guinea pigs, 8-12 months old and weighing 350-400 g, were each given a 9 mg/kg dose of DNOC in 0.5 ml of 0.9% NaCl solution ip six times/week over a period of 30 days. Twenty control guinea pigs were given injections of 0.5 ml of saline according to the same regimen. The guinea pigs were killed 24 hours after the last injection. Total sialic acid and amino sugar concentrations in the liver and in the serum were measured. Glycoprotein fractions of the serum were separated electrophoretically and measured, as was the DNOC concentration in the blood.

The authors [38] found that blood levels of DNOC in guinea pigs given injections of DNOC ranged from 21 to 32 $\mu$g/ml. No DNOC was found in the blood of the control guinea pigs. Amino sugar and sialic acid concentrations were significantly greater in the liver and serum of guinea pigs given DNOC than in the controls, and the glycoprotein concentrations of the albumin and alpha-2 globulin fractions of their serum were lower than in controls. The investigators also found increases in the

glycoprotein content of the serum alpha-1 and gamma globulin fractions and a slight increase in the glycoprotein content of the beta globulin fraction of the guinea pigs given DNOC. These findings suggested to the authors that DNOC might selectively block the synthesis of some glycoproteins while simultaneously increasing the production of those that contain high amounts of sugar, such as alpha-1 globulin.

Burkatskaya and Karpenko [39] investigated the effect of DNOC on white rats, especially on the levels of sodium and potassium in various tissues. Eighty rats weighing 150-200 g were divided into five groups and an unspecified number in one group were each given one oral dose of 50 mg of DNOC/kg of body weight. A group of 38 rats served as controls. The sex of the rats was not stated. Signs of intoxication were recorded for 2 hours after the dose was administered, and the animals were then killed. The authors measured the levels of sodium and potassium in the blood plasma, erythrocytes, myocardium, liver, and kidneys, the concentration of blood sugar, and the distribution of water in the myocardium and liver.

Toxic effects were observed in 30% of the rats that were given DNOC, but specific signs were not mentioned [39]. Both electrolyte levels were significantly higher ($P<0.05$) in the plasma and kidneys of the rats given DNOC than in the tissues from control animals. DNOC administration produced a significant decrease ($P<0.05$) in the potassium level in the myocardium and a significant increase ($P<0.05$) in the sodium content of the myocardium and liver. The concentrations of both elements in the erythrocytes and of potassium in the liver were unchanged. The rats were hyperglycemic after being given DNOC, but the actual blood sugar level was not specified. The authors found significant changes ($P<0.05$) in the

distribution of water in the cells. There was an increase in the intracellular water, a decrease in the extracellular water, and a decrease in the total water in the myocardium and liver following DNOC administration.

Many cases of cataract formation in people taking DNOC internally for weight reduction have been reported [7,12]. Because of this observation, Spencer et al [34] investigated the ability of DNOC to produce cataracts in animals. Ducklings had previously been found to be susceptible to developing cataracts following dinitrophenol exposure, and were therefore used in the experiment. A diet containing 0.25% DNOC was given to 8-10 2-week-old ducklings. Within 24 hours, all of the birds had developed cataracts, and by the next day they were all dead.

Only one report was found in the literature in which the mutagenic potential of DNOC was investigated. In 1972, Andersen et al [40] reported an evaluation of the ability of 110 herbicides, including DNOC, to produce point mutations in histidine-dependent mutants of Salmonella typhimurium, bacteriophage T4, and in two RII mutants of bacteriophage T4. The culture mediums were prepared by mixing freshly grown cultures of the mutants with soft agar and pouring into petri dishes. After the agar solidifed, DNOC was applied to the surface of each plate. They found that the mutation frequency rates produced by DNOC were no greater than the spontaneous rates. Although the data from this report indicate that DNOC is not mutagenic in a spot test, the experiment was not adequate for fully evaluating the mutagenicity of DNOC. The actual Salmonella strains were not identified and liver postmitochondrial activation systems were not utilized, thereby preventing consideration of possible activation of DNOC.

The success of the test relied on DNOC diffusing into the medium, since DNOC was not incorporated with the agar.

In several of the human studies described in this chapter, the investigators [6,8,10-13,17,19,21-23] have reported that one major effect observed in individuals exposed to DNOC is a large increase in the BMR. Some investigators have concluded that DNOC affects metabolism by uncoupling the oxidative phosphorylation process [21,22,41], resulting in increased cellular respiration (increased oxygen consumption) and decreased formation of adenosine triphosphate (ATP), which contains "high-energy" phosphate bonds. Therefore, energy generated in the body cannot be converted to its usual form (ATP) and is released as heat instead [33].

The effects of DNOC on the oxidative phosphorylation process have been investigated by both in vivo and in vitro techniques [42,43]. Muscatello et al [42] measured the rate of oxygen uptake and the activity of adenosine triphosphatase (ATPase) in liver mitochrondria taken from fasted male rats weighing 200-300 g. They found that DNOC at a concentration of 5 $\mu$M in a mitochondrial preparation produced a maximum increase in oxygen uptake and also increased ATPase activity.

Burkatskaya and Anina [43] gave rats, weighing 150-170 g, 75 mg/kg of DNOC orally and observed the effects on oxidative phosphorylation. As soon as the rats exhibited toxic effects, such as increased respiratory rate, they were killed. Another group of rats served as controls, but the control conditions were not specified. Livers were removed, and the concentration of ATP in liver tissue was determined. The ATP content was 188±21 $\mu$g of phosphorus/g of tissue in controls and 34±5 $\mu$g of phosphorus/g of tissue in rats exposed to DNOC.

Lehninger [44], in Biochemistry, states that uncoupling agents stimulate oxygen uptake and cause increases in the ATP-hydrolyzing activity. Increases in ATPase, as observed by Muscatello et al [42], would indicate that an increased rate of breakdown of ATP to adenosine diphosphate (ADP) is occurring.

Muscatello et al [42] also examined the ultrastructure of mitochondria by electron microscopy after DNOC was added to mitochondrial suspensions prepared from rat livers. They observed that DNOC caused the mitochondria to condense and form invaginations of the inner membrane and produced a significant decrease in the total volume of the mitochondria. However, since the authors found that other factors influenced mitochondrial configurations, they could not directly relate such changes to an uncoupling effect. The finding of configurational changes might be related to the coupling of oxidative phosphorylation that, according to one theory, occurs through conformational changes in the structure of the mitochondria [44].

(d) Metabolism

Several investigators have conducted experiments to determine the fate of DNOC after its administration to animals [45-47]. Urinary metabolites have been measured, and a detoxification pathway for DNOC has been suggested.

Truhaut and De Lavaur [45] reported on the metabolism of DNOC in rabbits. The compound was administered as an alkaline aqueous solution by gastric intubation to rabbits. Doses of 5, 10, 15, 18, and 20 mg/kg were administered to the rabbits, which had been fasted for 15 hours. The distribution of DNOC and its aminonitro metabolites was examined in the

blood, bone marrow, adipose tissue, kidneys, liver, brain, and urine within 7 hours after the dose was given.

When 10 and 15 mg of DNOC/kg were given to rabbits, the blood DNOC concentrations rose to 25 and 34 μg/g, respectively, and remained at those levels for 5-6 hours [45]. A dose of 18 mg/kg, which was fatal to the rabbit, produced a blood DNOC level of 50 μg/g. No amino derivatives were detected in the blood, the bone marrow, or the adipose tissue of the animals. However, 6-amino-4-nitro-o-cresol was detected in the liver, kidneys, and brain, while no 4-amino-6-nitro-o-cresol was found. It was concluded that the ratio of 6-amino-4-nitro-o-cresol to DNOC was a function of the dose of DNOC administered to the animal. When a low dose of DNOC (10 mg/kg) was given, little 6-amino-4-nitro-o-cresol was found in the kidneys, and none was in the liver and brain. As the dose of DNOC was increased, the ratio also increased, and it was especially high in the kidneys. An increase in the dose from 10 to 20 mg/kg raised the ratio in the kidneys from 0.42 to 5.29. Both DNOC and 6-amino-4-nitro-o-cresol were detected in the urine. When 10-15 mg/g were given, 25-38% of both metabolites were recovered in the urine. From 82 to 97% of this was eliminated in 24 hours, and the remainder in the next 2-3 days. As in the kidney, the ratio of 6-amino-4-nitro-o-cresol to DNOC in the urine increased as the dose of DNOC was increased, at least within the first 7 hours after the dose was administered. The ratios, measured 2.5-3.75 hours after doses of 10 and 20 mg/kg were given, were 0.66 and 1.47, respectively. The highest ratio measured was in a rabbit that died 3 hours after receiving DNOC. This animal was given an 18 mg/kg dose of DNOC, and the urinary ratio measured at the time of death was 2.40. Only small

amounts of 4-amino-6-nitro-o-cresol were detected in the urine. The authors considered the metabolism of DNOC to 6-amino-4-nitro-o-cresol a detoxification mechanism that plays an important role only when a toxic dose of DNOC is administered. They suggested that the ratio of 6-amino-4-nitro-o-cresol to DNOC might be a useful indicator in evaluating the severity of the exposure to DNOC.

The metabolic fate of DNOC in rabbits was also investigated by Smith et al [46]. Forty rabbits (sex and age not specified) were given 20-30 mg/kg of DNOC by stomach tube, and urine was collected from each for 2 days to measure metabolites. Three separate extracts of the urine samples were prepared, and metabolites were identified by paper chromatography and spectrophotometry.

Less than 20% of the dose of DNOC was recovered in the urine in 2 days [46]. Between 5 and 5.5% was excreted as free DNOC, and 0.7% as DNOC conjugates. The authors did not identify the conjugates more specifically. Most of the urinary metabolites (about 12% of the dose) were derivatives of 6-amino-4-nitro-o-cresol. About 1.5% of the dose was excreted as 6-acetamido-4-nitro-o-cresol and 9-10.6% as the hydroxyl group conjugate. Traces of 6-amino-4-nitro-o-cresol, 4-amino-6-nitro-o-cresol, and 3-amino-5-nitro-salicylic acid were also detected. The metabolic pathways of DNOC in the rabbit suggested by Smith et al are summarized in Figure XIII-1.

The authors [46] speculated that conversion of DNOC to 6-acetamido-4-nitro-o-cresol was the major detoxification pathway. They found that rabbits given 600 mg/kg of 6-amino-4-nitro-o-cresol or 2 g of 6-acetamido-4-nitro-o-cresol by stomach tube survived, while two rabbits died after being given 31 and 32 mg/kg of DNOC.

In 1970, Jegatheeswaran and Harvey [47] reported that the rumen microflora of sheep affect the metabolism of DNOC. In a preliminary experiment, they found that isolated rumen contents were able to reduce DNOC to 6-amino-4-nitro-o-cresol, which was then converted to 4,6-diamino-o-cresol. Separation of the rumen contents into three fractions (protozoa, bacteria, and cell-free supernatant) showed that only the first two fractions were able to reduce DNOC.

In a second experiment, 20 mg/kg of DNOC was given to one sheep by mouth and to another by ip injection [47]. Blood and urine samples were taken at various intervals for 3 days to measure the DNOC content. Administration by the ip route resulted in a tenfold greater serum level of DNOC than was produced by oral administration within hours of administration. The serum levels reached a peak in 4-6 hours, 110 μg/ml of serum for the ip route and 12 μg/ml of serum for the oral route. By 72 hours, the serum level was less than 10 μg/ml in both sheep. The type of metabolites found in the urine depended on the route of administration. Of the DNOC given by ip injection, 33.6% was accounted for in the urine, 3.7% as free DNOC, 7.2% as conjugated DNOC, 22.7% as conjugated 6-amino-4-nitro-o-cresol, and traces of 4,6-diamino-o-cresol. Of an oral dose, 30.6% was accounted for in the urine, 5.3% as conjugated 6-amino-4-nitro-o-cresol and 25.3% as 4,6-diamino-o-cresol.

## Correlation of Exposure and Effect

The available literature concerning humans indicates that DNOC is absorbed through the respiratory and gastrointestinal tracts and through

the skin and that it accumulates in the blood. The signs and symptoms of intoxication observed in individuals exposed to DNOC by these routes were often associated with increased metabolism [6,9-13,17,19,21-23]. Effects included profuse sweating, thirst, lassitude, malaise, headache, loss of weight, a sensation of heat, and an increased metabolic rate. In addition, peoples' skin, hair, sclera, and conjunctiva have been stained yellow [6,9-14,16,17,19,21,22,24]. Apparently, although this staining indicated that exposure to DNOC had occurred, it provided no measure of the extent of biologic impairment [17,22].

In evaluating studies on manufacturing and agricultural workers, it was often difficult to assess the impact of inhalation versus dermal exposure unless a worker was using protective equipment that prevented exposure by a particular route. In addition to the toxic effects associated with increased metabolism, other reported effects in workers included kidney damage [20], diarrhea [22], unspecified changes in the gastrointestinal tract [25] and in the cardiovascular system and peripheral blood [25], and CNS disturbances, such as confusion [24], loss of motor function in the legs [24], visual disturbance [20], tingling sensations in the limbs [23], unspecified changes in the central and autonomic nervous systems [25], and microscopic changes in the brain [14]. Because the DNOC air concentrations in these studies were only rarely reported, no dose-response relationship could be determined.

Bidstrup and Payne [6] observed the profound effect of environmental temperature on DNOC toxicity. They noted that the only deaths in workers from DNOC exposure in Great Britain occurred in what the authors considered "unusually hot" weather (56-86 F). Other investigators have also reported

that the toxicity of DNOC in humans is enhanced during warm weather [17,21,22]. Investigations in mice [36] and rats [33] given DNOC subcutaneously, in rats given DNOC by stomach tube [29], and in rabbits with DNOC applied to the skin [29] have verified the influence of temperature on DNOC toxicity. Increasing the environmental temperature resulted in a decrease in the LD50 [29,33] and a decrease in the LT50 [36]. The effects of environmental temperature on DNOC toxicity in animals are summarized in Table III-1.

Studies in various animal species also have confirmed the toxicity of DNOC in humans exposed by the inhalation and dermal routes. King and Harvey [29] reported that rats exposed to DNOC aerosol at a concentration of 100 mg/cu m for 4 hours had a decreased respiration rate during the exposure period and that body temperature decreased in some but increased in others. In cats exposed to DNOC aerosol at concentrations of 36-100 mg/cu m for 4 hours, effects included salivation, lacrimation, labored breathing, sluggishness, tremors, increases in body temperature, blood sugar concentration, and leukocyte count, and decreases in hemoglobin concentration, erythrocyte count, and catalase and peroxidase activities [25]. At similar concentrations, repeated exposure to DNOC was more toxic than a single exposure [25]. Changes in blood cell counts and in catalase and peroxidase activities, which were categorized by the author as slight and transient, were found in cats exposed for 2 or 3 months at a DNOC air concentration of 0.2 mg/cu m. In contrast, no effects were observed after a single 4-hour exposure at 0.4 mg/cu m.

Conflicting evidence has been reported concerning the effects of dermal absorption of DNOC when this was the only route of exposure. One

author observed no effects in volunteers who had a 2% aqueous solution of DNOC applied to their shaved armpits and forearms daily for 30 days [15]. However, other studies [16,21,23] have shown that DNOC is absorbed through the skin and can produce both local and systemic effects. DNOC has been found in the blood after dermal application [13,21], and toxic effects have been observed, including peripheral neuritis [23] and death [16].

Similarly, reports of effects on animals from dermal exposure to DNOC have been conflicting. No effects were noticed in rats or rabbits given DNOC as a 2% aqueous solution for 30 days [15] or in rabbits given a single dose of DNOC in dry form [26]. A single application of DNOC as a 3% aqueous suspension produced unspecified changes in respiration, cardiac activity, and temperature regulation in rabbits [26]. Single dermal applications of DNOC as aqueous solutions produced agitation, twitching, labored breathing, thirst, and loss of appetite in mice [31], and applications as alcohol solutions produced death in guinea pigs [34]. The above mentioned human and animal experimental data [16,21,23,26,31,34] taken together indicate that dermal exposure to DNOC can lead to adverse health effects.

In studies conducted to determine the kinetics of absorption and distribution patterns, DNOC has not been shown to accumulate in the blood of various animal species [29,33]. In rats and rabbits that were given two or more daily subcutaneous injections of DNOC, the serum levels on succeeding days were no higher than they were 24 hours after the first dose [33]. In dogs, the serum level rose for the first 3 days but then fell, even though two additional doses were given [33]. DNOC was also eliminated from the blood of animals faster than it was in humans [29,33]. Within 24

hours after a single subcutaneous injection of DNOC, it was almost completely eliminated from the serum of rabbits. It took 4 days to be cleared from the serum of rats and cats and 6 days from dogs [33]. DNOC accumulated only slightly in the blood when given to rats by stomach tube or ip injection and did not accumulate in the blood when given to rabbits by stomach tube [29].

Inhalation studies in rats [29] have confirmed that DNOC is absorbed through the respiratory tract into the bloodstream but does not accumulate in the blood. The inhalation data in one report [25] also corroborated the findings in animals exposed to DNOC by other routes [29,33] that DNOC is eliminated from animals more quickly than from humans.

Although few of the reports found indicated the concentration of airborne DNOC at which signs and symptoms of intoxication occurred in humans, several studies have associated blood DNOC levels with toxic effects [13,17,19-21] and have shown that, unlike in animals, DNOC accumulates in the blood of humans. In comparing studies on blood DNOC levels, certain precautions must be taken when correlating the results. It was reported that over 90% of the DNOC detected in the blood was found in the serum [33]. Therefore, a comparison of numerically similar blood DNOC levels expressed as weight/volume of serum with those expressed as weight/weight of whole blood can only be done by approximate conversions. A given DNOC serum level will have a lower value when expressed as the amount in whole blood.

Another factor considered in comparing results was the time after exposure when blood DNOC levels were determined. Because DNOC is eliminated slowly from the human body [13,17,19,21], blood DNOC levels did

not vary much in the first few days. However, if the time interval from exposure to sample collection is longer than a few days, a comparison of results might not be valid.

Only one report [26] found in the literature documented both the blood DNOC levels in workers and the concentration of DNOC in the air they breathed. Insufficient data are available to determine a correlation between these two factors. The average DNOC concentration in the blood of agricultural sprayers ranged from traces to 3.5 mg% (35 μg/ml), and the average DNOC air concentration in the breathing zone of these workers was 0.0036 mg/liter (3.6 mg/cu m). It was not reported whether there were any signs or symptoms of intoxication.

DNOC accumulated in the blood of five male volunteers who were given 75 mg of DNOC orally for 5 consecutive days [13]. The men experienced an exaggerated sense of well-being when blood levels were about 20 μg/g [17], and headache, lassitude, and malaise were associated with DNOC blood levels of 40-48 μg/g. DNOC was excreted slowly and was still detected in the blood 40 days after the last dose. Another study [21] showed that it took 2-8 weeks for DNOC to be cleared from the serum. In one of the few cases where DNOC in a patient's blood was monitored throughout his recovery period [19], the severity of the symptoms decreased as blood levels decreased.

Several studies of agricultural sprayers who used DNOC solutions have also ascertained that signs of intoxication are associated with blood DNOC levels greater than 20 μg/g [17,19-21]. Exposure was primarily by inhalation, but contact with the skin could not be ruled out. In those studies that allowed comparison of effects in several people, the authors

found that the most severely poisoned individuals of the group had higher blood DNOC levels than their less affected coworkers [17,20]. Workers who exhibited symptoms of intoxication and required hospitalization generally had blood DNOC levels of 20 μg/g or more [17,19-21]. In the reports found, the lowest blood DNOC level in an individual who died was 75 μg/g [17].

Most workers who had blood DNOC levels of less than 10 μg/g were not adversely affected [17,22,27]. There were a few exceptions [20,22,23], but in two of these cases, the investigators [20,22] considered the effects to be only mild. They reported that blood DNOC levels greater than 20 μg/g occurred with severe poisoning.

The data on blood DNOC levels in humans and accompanying effects are summarized in Table III-2. They indicate that workers with DNOC concentrations of 40 μg/g of whole blood (approximately 80 μg/ml of serum) or greater will most likely develop toxic effects. In addition, for the concentration range between 20 and 40 μg/g of whole blood, probably because of variation in individual susceptibility, some workers are affected and others show no adverse effects. Most workers with blood DNOC levels below 20 μg/g were not affected, although, again because of individual susceptibility, some exhibited mild effects.

The effects of DNOC exposure on humans and animals are summarized in Tables III-4 and III-5. In summary, the major effect of exposure to DNOC is a severely increased metabolic rate. Signs and symptoms of intoxication that accompany this effect include an exaggerated sense of well-being, an elevated BMR, profuse sweating, thirst, headache, malaise, and a sensation of heat. Other important effects observed in workers exposed to DNOC are nervous system and gastrointestinal disturbances and kidney damage.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No studies on the carcinogenic or teratogenic potential of DNOC were found in the literature.

The mutagenic potential of DNOC was tested in four different microbial test systems [40], and the mutation frequency rates were no higher than spontaneous rates. However, because of the previously mentioned inadequacies in the testing procedure, this report cannot be relied upon as conclusive evidence that DNOC is not mutagenic.

Vashakidze [37] investigated the effects of DNOC on the rat reproductive cycle. Although some unspecified effects on the reproductive glands and on the estrous cycle were reported, several shortcomings in the experimental design and presentation of the data prevent adequate assessment of the findings.

TABLE III-1

EFFECTS OF ENVIRONMENTAL TEMPERATURE
ON DNOC TOXICITY IN ANIMALS

| Route of Exposure | Species | Dose* (mg/kg) | Temperature | Mortality (%) | Reference |
|---|---|---|---|---|---|
| Oral | Rat | 40 | 20-22 C | 16.7 | 29 |
| " | " | 40 | 37-40 C | 100 | 29 |
| " | " | 20 | 20-22 C | 0 | 29 |
| " | " | 20 | 37-40 C | 50 | 29 |
| Subcutaneous | " | 27.7 | 5-10 C | 50 | 33 |
| " | " | 24.8 | 18-20 C | 50 | 33 |
| " | " | 19.2 | 36-37 C | 50 | 33 |
| " | " | 20 x36-45 d | cool | 8.5 | 33 |
| " | " | 20 x20 d | " | 6.5 | 33 |
| " | " | 20 x10 d | " | 3.6 | 33 |
| " | " | 20 x17 d | warm | 31 | 33 |
| | | | | LT50** | |
| " | Mouse | 20 | 10 C | 59.0 min | 36 |
| " | " | 20 | 20 C | 51.3 min | 36 |
| " | " | 20 | 40 C | 18.8 min | 36 |

*Single dose unless specified
**Time to death of 50% of animals

TABLE III-2

RELATIONSHIP OF BLOOD DNOC LEVELS AND EFFECTS IN HUMANS

| Route of Exposure | No. | Occupation | Concentration | Time of Measurement* | Blood DNOC Level (μg/g) | Effects | Reference |
|---|---|---|---|---|---|---|---|
| Inhalation Dermal | 1 | Agricultural worker | "Dense mist" | 33 hr | 1,000**S | Death | 21 |
| " | 1 | " | - | 1 wk | 200**S | Sweating, labored breathing, vomiting | |
| " | 1 | " | - | - | 75 | Death | 17 |
| " | 1 | " | - | 52 hr<br>7 d | 60<br>25 | Headache, lassitude, BMR 275% at 52 hr | 19 |
| " | 1 | " | - | - | 60**S | Sweating, headache, labored breathing, fatigue | 21 |
| " | 1 | " | - | 24 hr | 55 | Unconsciousness | 20 |
| " | 2 | " | - | - | 44-55 | Acute poisoning | 17 |
| Oral | 5 | Experimental subjects | 1.0-1.3 mg/kg/d x 5 d | 120 hr | 40-48 | Headache, lassitude, malaise | 13 |
| Inhalation Dermal | 4 | Agricultural workers | - | 24 hr | 20-40** | Liver damage | 20 |
| " | 5 | " | - | - | 30-40 | No effects | 17 |
| " | 6 | " | - | 24 hr | 21-40** | Moderate poisoning; recovery period longer than 8 d | 20 |
| " | 32 | " | - | " | 7-37** | Mild poisoning; recovery within 8 d | 20 |
| " | 1 | " | - | " | 30** | Fever | 20 |
| " | 16 | " | - | - | 20-30 | No effects | 17 |
| " | 1 | " | - | 24 hr | 25** | Kidney damage | 20 |

TABLE III-2 (CONTINUED)

RELATIONSHIP OF BLOOD DNOC LEVELS AND EFFECTS IN HUMANS

| Route of Exposure | No. | Occupation | Concentration | Time of Measurement* | Blood DNOC Level (μg/g) | Effects | Reference |
|---|---|---|---|---|---|---|---|
| Oral | 5 | Experimental subjects | 1.0-1.3 mg/kg/d | 96 hr | 20 | Exaggerated feeling of well-being | 13 |
| Inhalation Dermal | 21 | Agricultural workers | - | - | 10-20 | No effects | 17 |
| " | 2 | Manufacturing workers | 20% in oil | 1 wk | 8-17 | Paresthesia | 23 |
| " | 149 | Agricultural workers | - | - | <10 | No effects | 17 |
| " | 4 | " | - | 24 hr | 4-9**S | Sweating, thirst | 22 |
| " | 23 | " | - | 24 hr | 1-8**S | No effects | 22 |
| " | 1 | " | - | 3 wk | <5**S | Fatigue | 21 |
| " | - | " | - | 24 hr | 1-4 | No effects | 27 |

*Time from end of exposure to blood DNOC determinations
**Reported as μg/ml
S indicates serum or plasma DNOC level

TABLE III-3

RELATIONSHIP OF BLOOD DNOC LEVELS AND EFFECTS IN ANIMALS

| Route of Exposure | No. | Species | Dose or Concentration | Exposure Duration | Time of Measurement and Blood DNOC Level | Effects | Reference |
|---|---|---|---|---|---|---|---|
| Inhalation | 6 | Rats | 100 mg/cu m | 4 hr | -3 -1 0* 20 hr<br>4-50 9-42 6-64 17-29 g/ml | Increased respiration | 29 |
| " | 12 | Cats | " | " | 0 hr 60-15 g/ml | Death of 4; blood and autonomic nervous system changes | 25 |
| " | 3 | " | 60 mg/cu m | " | 24 hr 100-150 g/ml | No deaths | 25 |
| " | 3 | " | 40 mg/cu m | " | 0 hr 40 g/ml | Death of 1; blood and autonomic nervous system changes | 25 |
| " | 3 | " | 1.4 mg/cu m | " | Time not reported; No DNOC detected | No deaths | 25 |
| " | 3 | " | 2 mg/cu m | 4 hr/d x 30 d | " " | Death of 2 | 25 |
| " | 3 | " | 0.2 mg/cu m | 4 hr/d x 2-3 mon | " 10-20 g/ml | No deaths; transient blood changes | 25 |
| Subcutaneous | - | | | | 0 1 2 3 4 5 6 d | | 38 |
| | | Rats | 10 mg/kg | 1 dose | 82 36 8 3 T - - g/ml | Not reported | |
| " | - | Cats | " | " | 80 36 18 8 3 - - g/ml | " | |
| " | - | Dogs | " | " | 56 40 20 - 3 - T g/ml | " | |
| " | - | Rabbits | " | " | 73 T - - - - - g/ml | " | |
| " | - | Rabbits | " | 1 dose | 1 3 5 24 hr<br>2-25 50-90 25-60 0-8 g/ml | " | |

*Immediately after exposure

TABLE III-4

EFFECTS OF OCCUPATIONAL EXPOSURE TO DNOC

| Occupation (Mean Concentration DNOC in Air) | Exposure Duration | Exposed Workers | | | Effects | Reference |
|---|---|---|---|---|---|---|
| | | No. | Age | Sex | | |
| Agriculture (-) | - | 2 | - | M | Brain hemorrhage, death | 14 |
| " | 2 d | 3 | 17-21 | M | Labored breathing, tachycardia, thirst, sweating, 1 death | 24 |
| " | 6 wk (summer) | 133 | - | M | Intoxication in 4, 1 death | 17 |
| " | 5 wk | 1 | 27 | M | Headache, elevated BMR | 19 |
| " | up to 4 mon | 5 | 25-40 | M | Nausea, thirst, sweating, 1 death | 21 |
| " | 1 d | 47 | 15-44 | F | Fever, unconsciousness, liver and kidney damage | 20 |
| Agriculture (0.7 mg/cu m) | - | - | - | - | Changes in blood and autonomic nervous system | 25 |
| Agriculture (3.6 mg/cu m) | - | 20 | - | - | No effects | 26 |
| Agriculture (-) | 50 d (winter) | 39 | - | M | " | 17 |
| Manufacturing (-) | 5-30 d | 27 | 24-48 | M | Elevated BMR, sweating, mucosal irritation | 22 |
| Manufacturing (0.9 mg/cu m) | - | - | - | - | Cardiovascular, CNS, and gastrointestinal effects | 25 |
| Manufacturing (-) | 6 wk-5 yr | 23 | - | M | No effects | 17 |
| Maintenance (-) | 17 d-2 mon | 2 | 24,47 | M | Paresthesia | 23 |

TABLE III-5

EFFECTS OF DNOC EXPOSURE IN ANIMALS

| Route of Exposure | Species | Exposure Concentration | Exposure Duration | Effects | Reference |
|---|---|---|---|---|---|
| Inhalation | Rat | 100 mg/cu m | 4 hr | Decreased respiration | 29 |
| " | Cat | 100 mg/cu m | " | Death in 4 of 12; autonomic nervous system effects; blood changes | 25 |
| " | " | 60 mg/cu m | " | No deaths; other effects as at 100 mg/cu m | 25 |
| " | " | 40 mg/cu m | " | Death in 1 of 3; other effects as at 100 mg/cu m | 25 |
| " | " | 2.0 mg/cu m | 4 hr/d 1 mon | Death in 2 of 3; blood changes, weight loss | 25 |
| " | " | 1.4 mg/cu m | 4 hr | No effects | 25 |
| " | " | 0.2 mg/cu m | 4 hr/d 2-3 mon | No deaths; transient blood changes | 25 |
| Dermal | Rat | 2% | 30 d | No effects | 15 |
| " | Mouse | 187 mg/kg | 1 dose | LD50 | 31 |
| " | Rabbit | 500 mg/kg | " | Changes in respiration and heart rate | 26 |
| " | " | 500 mg/kg | " | No effects | 26 |
| " | " | 1,000 mg/kg | " | LD50 | 26 |
| " | " | 2% | 30 d | No effects | 15 |
| " | Guinea pig | 500 mg/kg | 1 dose | 100% mortality | 34 |
| " | " | 200 mg/kg | " | No deaths | 34 |

TABLE III-5 (CONTINUED)

EFFECTS OF DNOC EXPOSURE IN ANIMALS

| Route of Exposure | Species | Exposure Concentration | Exposure Duration | Effects | Reference |
|---|---|---|---|---|---|
| Oral | Rat | 85 mg/kg | 1 dose | LD50 | 26 |
| " | " | 40 mg/kg | " | Death in 2 of 12 | 29 |
| " | " | 30 mg/kg | " | Minimum lethal dose | 15 |
| " | " | 20 mg/kg | " | No effects | 29 |
| " | " | 0.005 mg/kg/d | 2 mon | " | 30 |
| " | Mouse | 47 mg/kg | 1 dose | LD50 | 26 |
| " | " | 16.4 mg/kg | " | " | 31 |
| " | Hare | 24.8 mg/kg | " | " | 32 |
| " | Cat | 50 mg/kg | " | " | 26 |
| " | Pheasant | 8.4 mg/kg | " | " | 32 |
| " | " | 7.1 mg/kg/d | 3 d | " | 32 |
| " | Partridge | 11.1 mg/kg/d | " | " | 32 |
| " | " | 8.3 mg/kg | 1 dose | " | 32 |
| Sub-cutaneous | Rat | 26-39 mg/kg | " | " | 35 |
| " | " | 20 mg/kg | " | Minimum lethal dose | 15 |
| " | " | 15 mg/kg/d | 30 d | Slight weight gain | 15 |
| " | Mouse | 24.2 mg/kg | 1 dose | LD50 | 33 |

# IV. ENVIRONMENTAL DATA

## Sampling and Analytical Methods

Few reports of methods studied for their efficiency in collecting DNOC in air have been found. Kurchatova [48] suggested the use of a cotton filter, designated as FPP-15, in series with an absorber containing 5 ml of a 1% solution of sodium hydroxide. He did not provide information regarding the efficiency of the sampling method.

Methods that have been tested for their effectiveness in the determination of DNOC in air samples include spectrophotometry, thin-layer chromatography, and gas chromatography. Kurchatova [48] suggested using spectrophotometry in the visible range to quantitatively determine DNOC from an air sample. A peak wavelength of 370 nm was obtained from an alkaline solution of DNOC. Separate measurements were made for the quantity of DNOC vapor absorbed in sodium hydroxide and for the DNOC on the filter. The material on the filter was eluted with hot sodium hydroxide before it was analyzed. The author did not discuss the possibility of interfering substances and provided no data that permit assessment of the accuracy of the method.

Kurchatova [48] recommended thin-layer chromatography for separating dinitrophenolic compounds and for qualitatively determining the presence of DNOC. After separation of the compounds, quantitative measurement of DNOC could be done spectrophotometrically.

In addition to the sampling and analytical procedures described above, NIOSH has investigated alternative methods. Two air sampling

methods for DNOC have been tested. Activated charcoal tubes, as described in NIOSH Method No. P and CAM 127 [49], have been used as a collection medium. The precision of this method for collecting DNOC was not discussed, but it is expected that desorption of DNOC would be a difficult procedure. Further work by NIOSH indicated that, in the experiment conducted at room temperature, DNOC existed as a mixture of 75-80% particulate and 20-25% vapor [50]. However, under other experimental conditions or in the workplace, the proportions could be entirely different. Imprecise results were obtained from attempts to sample this type of environment at a rate of 1.5 liter/minute with a glass-fiber filter attached to the inlet of a midget bubbler containing 10 ml of 0.1 M sodium hydroxide. However, the investigators [50] did not determine whether the problem was in the sampling method itself or in the method used to generate the DNOC sample.

NIOSH evaluated two methods for determining the concentration of DNOC in air samples [50]. After sampling by adsorption on charcoal, desorption with acetone and analysis by gas chromatography with a flame ionization detector gave clearly defined peaks but lacked adequate sensitivity. Analysis by gas chromatography with an electron-capture detector might provide increased sensitivity. For this analysis, desorption from charcoal with a suitable solvent, such as 10 ml of 99:1 benzene-methanol (v/v), would be required.

NIOSH found that a spectrophotometric method based on a spectral absorption at 395 nm yielded satisfactory results [50]. The NIOSH Validation Report [50] indicated that the coefficient of variation for the analytical phase of the test, CV1, was 0.027 at the 0.2 mg/cu m level. The

coefficient of variation of the sampling phase, CV2, was 0.169 (with no mention of sampling bias error). Assuming a coefficient of variation of the sampling pump to be 0.05, the calculated coefficient of variation of the total sampling and analytical procedure, CV6, is 0.177. Therefore, the absolute total error at the 95% confidence limit, would be at least ±35% based on the formula:

$$CV6 = \frac{\text{total error (\%)}}{1.96}$$

Although the method involving sampling by glass-fiber filter and midget bubbler and analysis by spectrophotometry has not been fully evaluated by NIOSH and the sampling bias has not been accurately determined, NIOSH believes this method is the best available. Therefore, pending further research, these are the recommended sampling and analytical methods, and they are fully described in Appendices I and II.

## Biologic Monitoring Methods

Experimental techniques have been developed that permit accurate determination of the DNOC levels in the blood. Mikolajek [51] described a polarographic method. A standard solution containing DNOC in a buffer at pH 7.0 was mixed with 1 ml of blood, and then 0.01 N potassium chloride, methanol, and a buffer solution of pH 7.0 were added. One drop of n-octanol was added, and oxygen was purged with nitrogen before DNOC was determined polarographically in a range of potentials from -0.2 to 1.2 volts. The sensitivity of the method to interference from other compounds was not discussed.

Parker [52] first described a colorimetric procedure for the quantitative determination of DNOC in biologic fluids, including blood and urine. The method was based on a determination of the absorbance of the yellow color obtained when a methyl ethyl ketone extract of DNOC was treated with sodium carbonate.

Fenwick and Parker [53] found that beta-carotene could interfere with the ketone extract and modified the original Parker method [52] accordingly. The methyl ethyl ketone extract of DNOC was yellow in alkaline solution and colorless in acid, while the extract of beta-carotene retained the same color in acid and in alkali. Therefore, concentrated hydrochloric acid was added to the alkaline extract, and the amount of DNOC was determined from the difference in the absorbance before and after the acid was added.

Edson [54] suggested a simplified method for field measurements, which was similar to that of Parker [52] except that, instead of the absorbance being measured in a spectrophotometer, the color of the extract was visually compared to a series of nine standards containing various concentrations of DNOC. The lower limit of sensitivity of the method was 5 μg of DNOC/ml of whole blood.

NIOSH recommends that the method described in Appendix III, which is based on the techniques described by Parker [52] and Fenwick and Parker [53], be used for the biologic monitoring of DNOC.

Environmental Levels

Only a few reports were found in which investigators [18,25,26] recorded the concentrations of DNOC in workplace air. However, the

sampling and analytical procedures used were discussed in none of these, and the reports provided no information that could be of value in making recommendations for the environmental monitoring of DNOC.

## Engineering Controls

Engineering controls should have as their main objective keeping concentrations of airborne DNOC vapor and aerosol as low as possible, minimizing skin contact, and preventing explosions. In DNOC manufacturing and formulating areas, closed systems under negative pressure, when properly operated and maintained, are the best method of controlling concentrations of airborne DNOC and preventing exposure. When closed systems are not feasible, well-designed local exhaust ventilation systems are also effective. Ventilation systems are needed at loaders, blenders, mixers, mills, packaging equipment, and at all other potential sources of vapor, spray, or dust containing DNOC. Recommendations for appropriate ventilation systems are found in NIOSH Recommended Industrial Ventilation Guidelines [55], Industrial Ventilation-A Manual of Recommended Practice [56], published by the American Conference of Government Industrial Hygienists, and in Fundamentals Governing the Design and Operation of Local Exhaust Systems, Z9.2-1971 [57], published by the American National Standards Institute. In addition, since DNOC dust can form explosive mixtures with air, the National Fire Protection Association Codes on combustible dusts (NFPA N. 63-1971) and blower and exhaust systems (NFPA N. 91-1973) should be followed. Ventilation systems should be inspected and maintained regularly to ensure effective operation. Changes in process

that may affect the ventilation system should be assessed promptly to make certain that workers are adequately protected.

Since closed systems and local exhaust ventilation are not feasible for field application of DNOC, other engineering controls should be employed to prevent or minimize exposure. The use of air conditioned spray rig cabs with temperature and contaminant control, spraying equipment that produces coarse droplets instead of finely atomized sprays, and agitators that keep DNOC in suspension to prevent nozzle clogging will reduce the likelihood that workers will come in contact with DNOC.

# V. WORK PRACTICES

Experience indicates that the major routes of worker exposure to DNOC are by inhalation and dermal absorption [6,14,17-25]. Work practices should therefore be implemented to prevent or minimize exposure by these routes. Because the sources of DNOC and the likelihood of exposure will vary, depending on whether DNOC is being manufactured, formulated, or applied in agriculture, the work practices should fit the exposure situation.

(a) Work Practices for Manufacture and Formulation of DNOC

Exposure by inhalation can lead to adverse respiratory and systemic effects. Compliance with the recommended permissible exposure limit should protect workers against adverse health effects from inhalation of DNOC. Whenever feasible, operations, processes, and materials should be enclosed to reduce the accumulation of airborne concentrations of DNOC. These systems should be inspected frequently for leaks or damage, and any needed repairs should be made promptly. Although enclosure of systems is the recommended means of protection, during certain operations when the environmental limit is temporarily exceeded, respirators with suitable particulate canisters may be permitted. Any devices provided must meet the specifications of Table I-1.

A respiratory protective program in accordance with 29 CFR 1910.134 must be followed to ensure that respirators are routinely inspected and properly cleaned, maintained, and stored. Respiratory protective devices

should be decontaminated after each use and discarded when signs of deterioration are evident.

DNOC can also irritate the skin and eyes and cause severe systemic effects when it is absorbed through the skin [16,23]. Therefore, protective clothing must be worn by workers who handle these compounds. The degree of protection required depends on the severity of the potential exposure. Operations in which an aerosol may be generated require coveralls, gloves, and face shields (8-inch minimum) with goggles to prevent contact of DNOC with any part of the body, including the eyes. For jobs in which there is a possibility of the body being wetted with DNOC, full-body suits are necessary to adequately protect skin and eyes. Employees involved in operations in which splashes to the face or body may occur can be adequately protected with face shields (8-inch minimum), coveralls, aprons, and gloves. When exposure is limited to the handling of contaminated equipment or to handling small amounts of material that are unlikely to be splashed, coveralls and gloves should afford sufficient protection.

In one report [21] it was stated that rubber and plastic gloves afford protection from DNOC, but a case was cited of high blood DNOC levels in one worker even though he used such gloves. Therefore, protective equipment made of rubber or plastic should be used only if the manufacturer of the equipment states, or experience has shown, that it will offer sufficient protection from DNOC. Protective clothing and equipment should be decontaminated before reuse, and any protective apparel showing signs of deterioration should be discarded in clearly labeled, closed containers.

Emergency showers and eyewash fountains must be available in all work areas where DNOC is manufactured or formulated. Severe injury to the eyes can be prevented by immediate use of eyewash fountains. DNOC is also absorbed through the skin and will produce systemic effects [16,23]. Therefore, it is important that emergency showers be readily available so that DNOC can be immediately removed from the skin.

Ingestion of DNOC can be fatal [14]. A good sanitation program, safe work practices, and good personal hygiene will reduce the risk of exposure by this route. If eating areas are provided, they should be separate from all areas where DNOC is manufactured, formulated, used, or stored. Food and beverage consumption and smoking must be prohibited in any area where there is occupational exposure to DNOC.

DNOC should be stored in closed containers in cool, well-ventilated areas away from heat and strong oxidizing agents. Damaged drums or other containers for storage or transportation should be repaired only after they have been thoroughly purged with steam, flushed with water, and air dried.

DNOC is a combustible solid, and its dust may form explosive mixtures with air [4]. The National Fire Protection Association Code on combustible dusts (NFPA N.63-1971) should be followed. Because of the possibility of fire or dust explosion, all ignition sources must be controlled wherever DNOC is present. Foam, dry chemical, or carbon dioxide extinguishers should be used in the event of fire.

Spills of DNOC must be cleaned up immediately. Only properly trained and adequately protected employees should take part in cleanup operations. The area of a spill should be posted and secured to prevent entry by unauthorized personnel. Liquid DNOC formulations can be absorbed in

vermiculite, dry sand, earth, or other suitable material. If sufficient drainage to a suitable collection basin is available, spilled liquid can be hosed away with large quantities of water. Spilled solid material should be collected and deposited in a sealed container, and the area of a spill should be ventilated to remove any vapor or aerosol. Methods of waste disposal must comply with federal, state, and local regulations.

Maintenance and repair workers, especially those working on ventilation systems or in enclosed environments, have a high risk of exposure. To minimize or prevent exposure, they must be familiar with the hazards of the materials and with proper work practices, and they must have adequate supervision. Special precautions must be taken when work is to be performed in confined spaces. Entry into confined spaces should be controlled by a permit system. Prior to entry, all sources of DNOC must be sealed off and the equipment used for handling DNOC must be purged and tested for oxygen deficiency and for the presence of flammable vapors and toxic gases. Purging should be done with steam and followed by flushing with water. Continuous ventilation of the confined space should be maintained throughout the entry period. Personnel entering confined spaces should wear protective clothing, be equipped with a safety harness and lifeline, and use either a self-contained, pressure-demand mode breathing apparatus or a combination supplied-air suit with an auxiliary self-contained air supply. Anyone entering a confined space should be observed by a properly trained and equipped standby worker familiar with emergency procedures, in case rescue is necessary. A communication system should be set up among workers involved in the operation.

(b) Work Practices in the Application of DNOC

Agricultural spraying is a major source of occupational exposure to DNOC. Due to the nature of the spraying process, relatively high concentrations of airborne DNOC may be generated. Such concentrations may be hazardous, and spray personnel must be protected. Therefore, unless it can be shown by frequent industrial hygiene surveys that the DNOC air concentration does not exceed the permissible exposure limit, respiratory devices as specified in Table I-1 should be used to protect against inhalation of airborne DNOC. Full facepieces, helmets, or hoods may be used only if adequate coverage of exposed portions of the head and face is assured by the use of supplemental headgear. Half-mask respirators or other respiratory protective devices that do not afford eye protection must not be used because DNOC may irritate the eyes.

Wolfe [58] has stated that over 97% of most pesticides that contact the body during occupational exposure are deposited on the skin. Investigations of spray operators who used DNOC as a blossom-thinning agent showed that the average dermal exposure was 63.2 mg/hour [27]. Because of this demonstrated deposition of DNOC on skin surfaces and because it has been shown that skin contact with DNOC can lead to adverse health effects [16,23], protective clothing and equipment should be used by DNOC applicators.

All personnel occupationally exposed to DNOC should wear freshly laundered coveralls or work uniforms (long pants and long-sleeved shirts) [59]. If the coveralls or uniforms might become wetted by mist or spray use of a waterproof raincoat should provide the best protection for the upper back, shoulders, and forearms [58], but this may cause discomfort or

even heat stress in a hot environment. In such environments, wearing long-sleeved, water-repellant or waterproof clothing that will not be easily penetrated by the pesticide should provide a significant measure of protection [58].

Protection of the lower trunk and legs from contamination is important where the potential exists for liquid spillage, soaking by continued contact with sprays or sprayed foliage, or penetration of clothing through excessive contact with DNOC. Waterproof trousers will provide the best protection for the lower trunk and legs [58]. Even though the coveralls or uniforms are covered by waterproof protective clothing, daily bathing after work and daily changes to freshly laundered clothing are important for minimizing percutaneous absorption [58].

The head and neck should also be protected from contact with DNOC. Therefore, some type of protective headgear, such as waterproof rainhats and washable safety hardhats and caps, should be worn. Waterproof or water-repellant parkas may also be used to protect the head and neck at the same time [59]. Personnel potentially exposed to downward drifts of DNOC should wear wide-brimmed, water-repellant or waterproof hats to obtain additional protection for the head and neck areas [58].

Workers handling concentrated wettable powders, concentrated liquids, or finely divided dust formulations should wear protective gloves of natural rubber, neoprene, or plastic, although the permeability of these materials to DNOC remains to be determined. Contact of wet skin with DNOC should be avoided to minimize absorption.

If an employee comes in contact with concentrated formulations, his hands will often receive the highest exposure. Because they cover the

wrist area not normally protected by the sleeve, unlined rubber gauntlet gloves provide the best protection [58]. These gloves can be turned wrong side out for proper cleaning of the inside surface.

Use of waterproof footwear is necessary to minimize exposure when the DNOC formulation may wet the feet [58]. Footwear should be washed and dried thoroughly, inside and out, as frequently as necessary to remove DNOC.

Although development of cataracts following ingestion of DNOC has been reported [7,11,12], there is no evidence to suggest that eye exposure to DNOC causes cataracts. However, because DNOC can be irritating to the eyes [4], it is recommended as a minimum that all employees engaged in spraying DNOC or who might encounter DNOC spray or dust drift wear safety goggles. Face shields (8-inch minimum) with goggles should provide adequate protection for employees who handle the liquid pesticide.

To minimize absorption of DNOC through ingestion, employees should not eat, drink, or smoke in any area where there is a potential for occupational exposure to DNOC.

The employer is responsible for proper disposal of surplus pesticides and pesticide containers [60]. The Environmental Protection Agency has established regulations defining prohibited procedures pertinent to the disposal of surplus pesticides and containers (40 CFR 165, published in the Federal Register 39:3686 7-70, October 15, 1974). Specifically, open dumping is prohibited, and water dumping is generally prohibited. Open burning is also prohibited, except for small quantities, in combustible containers, not to exceed 50 pounds or the quantity emptied in a single workday, whichever is less. Such open burning may be performed only where

it is consistent with federal, state, or local ordinances. "Open burning" means the combustion of a pesticide, pesticide container, or pesticide-related waste in any fashion other than by incineration in a pesticide incinerator (40 CFR 165, published in the Federal Register 39:3686 7-70, October 15, 1974). Applicable local, state, and federal regulations should be consulted; if such regulations do not exist, suggested precautions include disposing of DNOC by incineration or burial. Incineration or burial should be performed in a manner not contributing to air or water pollution.

Since agricultural spraying often occurs during hot weather when full-body protective clothing might cause discomfort to workers, controls other than respiratory devices and full-body suits that are equally effective may be employed. If spraying can be done by aircraft or by other motorized vehicles, such as tractors with enclosed air-conditioned cabins, full-body protection is not necessary. The air-conditioned cabins should be frequently monitored to ensure that DNOC air levels are not exceeding the permissible occupational exposure limit. When air or ground vehicles are used to apply DNOC to fields, employees should not direct them through the drift of the spray or operate them where wind creates a drift hazard to themselves or others.

(c) Employee Education

Employee education on the safe handling of DNOC and its hazards is essential if injury and disease are to be prevented. It is particularly important that employees be informed of the dangers of skin contact with these compounds. The importance of the immediate removal of contaminated clothing and the use of liberal amounts of water to remove the compound

from the skin or eyes must be stressed. Workers potentially exposed to DNOC must be made aware of the signs and symptoms associated with DNOC intoxication and of the similarity of these effects to those produced by hot weather. Employees should be encouraged to contact medical personnel immediately if symptoms occur. Workers must also be informed that, because the toxicity of DNOC is increased in hot weather, extra care is necessary under these conditions to prevent injury.

In all workplaces where there is occupational exposure to DNOC, written instructions informing employees of the particular hazards of these chemicals, proper handling methods, procedures for cleaning up spilled material, personal protective equipment to be worn, and procedures to be used in emergencies must be on file and available to employees. The Material Safety Data Sheet shown in Appendix IV may be used as a guide for employers in providing the required information.

# VI. DEVELOPMENT OF STANDARD

## Basis for Previous Standards

In 1949, the American Conference of Governmental Industrial Hygienists (ACGIH) [61] recommended a Threshold Limit Value (TLV) for DNOC of 0.2 mg/cu m, based on experience with the compound in industrial plants. This value represented a TWA concentration limit for an 8-hour workday. A "skin" notation was added to the TLV in 1962 because DNOC could be absorbed through the skin [62]. The recommended TLV for DNOC remains at 0.2 mg/cu m [63].

The ACGIH [63] has recommended that a Threshold Limit Value-Short Term Exposure Limit (TLV-STEL) for DNOC be set at 0.6 mg/cu m. This value was defined as the "maximal concentration to which workers can be exposed for a period up to 15 minutes continuously without suffering from (1) irritation, (2) chronic or irreversible tissue change, or (3) narcosis of sufficient degree to increase accident proneness, impair self-rescue, or materially reduce work efficiency, provided that no more than four excursions per day are permitted, with at least 60 minutes between exposure periods, and provided that the daily TLV-TWA also is not exceeded."

The 1974 Documentation of Threshold Limit Values for Substances in Workroom Air [64] cited four reports that dealt with the toxicity of DNOC in animals and humans in support of the recommended TLV. Harvey et al [13], in a study of five volunteers, demonstrated that repeated daily ingestion of 75 mg of DNOC resulted in its considerable accumulation in the body. They found that symptoms of toxicity began to appear when blood DNOC

levels exceeded about 15-20 μg/g, a level attained after 5-7 days of ingestion. Volunteers suffered from lassitude, headache, and malaise. Fairhall [1] gave an account of an occupational DNOC poisoning that was originally described in the Baltimore Health News [18]. A worker had been exposed to airborne DNOC dust at a concentration of 4.7 mg/cu m. He was hospitalized with a temperature of 102 F, a BMR of over 400% of normal, rapid pulse and respiration, profuse sweating, shortness of breath, and cough. Fairhall [1] stated that reduction of the DNOC air concentration to 2.5 mg/cu m achieved satisfactory working conditions. However, the original report [18] did not indicate the effect of the reduction of the DNOC air concentration on the worker's health. Spencer et al [34] conducted feeding studies in various animal species to determine the toxicity of DNOC. The oral LD50 in rats was determined to be 31 mg/kg. Rats fed a diet containing 100 ppm of DNOC for 6 months showed no appreciable effects as determined by gross and microscopic examinations. Higher concentrations did, however, produce toxic effects. Ambrose [15] reported that 60% of young rats fed diets containing 125 ppm of DNOC died.

The ACGIH [64] concluded that the limit of 0.2 mg/cu m for DNOC "can be shown to be based on calculations that take into account the recognized accumulation from long-repeated, daily dosage and in addition appear to offer an extraordinarily large factor of safety." No reference was cited to support this statement.

The present Federal standard (29 CFR 1910.1000) for workplace exposure to DNOC is an 8-hour TWA concentration limit of 0.2 mg/cu m with a "SKIN" notation. This standard is based on the TLV for workplace exposure adopted by the ACGIH in 1968.

Finland, Poland, Rumania, and Yugoslavia have adopted Maximum Allowable Concentrations (MAC's) for DNOC that are numerically the same as the United States' [65]. Bulgaria and the Soviet Union have set limits of 0.05 mg/cu m, while Hungary limits exposure to 0.1 mg/cu m but permits exposure at twice that concentration for up to 30 minutes [65].

## Basis for the Recommended Standard

(a) Permissible Exposure Limits

Most of the deaths and injuries attributed to DNOC toxicity have occurred where exposure has probably been by both the inhalation and dermal routes [6,14,17,19-24]. Other reports [9-14] indicate that toxic effects can also result from ingestion of DNOC. The predominant signs and symptoms of DNOC intoxication include profuse sweating, thirst, lassitude, malaise, headache, loss of appetite, sensation of heat, and increased BMR. Exposure to DNOC also causes a yellow pigmentation of the skin, hair, sclera, and conjunctivae. Observations have shown that such staining is no more than an indication of exposure [22].

Deaths and injuries related to the manufacture and use of DNOC have occurred in several countries, but most such incidents have involved agricultural workers [6,14,17,19-24]. Affected workers had severely elevated BMR's accompanied by signs and symptoms that were associated with increased metabolism. Other toxic effects included kidney damage [20], peripheral neuritis [23], and CNS disturbances, such as confusion [24], loss of motor function in the legs [24], and visual disturbances [20]. Concentrations of DNOC in air were not specified in any of the reports,

although the major route of its entry into the body in most cases was believed to have been by inhalation, with skin absorption also being an important route. Most investigators [17,19-24] indicated that blood DNOC levels were associated with the severity of intoxication.

The concentrations at which airborne DNOC has produced specific blood levels of DNOC in exposed workers have only rarely been reported. In one such study [26], 13 of 20 workers involved in preparing a 1% solution of DNOC and loading it into sprayers had an average blood DNOC level of 3-5 mg% (30-50 μg/ml), and 7 had concentrations ranging from traces to 2 mg% (20 μg/ml). The average air concentration of DNOC in the respiratory zone of these workers was 0.0036 mg/liter (3.6 mg/cu m). Since DNOC concentrations close to those determined in the blood of these workers have been associated with the onset of illness [13,17], repeated exposure at a concentration of 3.6 mg/cu m would probably be detrimental to worker health. The author, however, did not state whether any signs or symptoms of intoxication were observed.

Only one study [25] was found in which DNOC air concentrations were measured and were associated with toxic effects. Exposures to airborne DNOC at concentrations that averaged 0.0009 mg/liter (0.9 mg/cu m) produced unspecified changes in the cardiovascular system, the central and autonomic nervous systems, the gastrointestinal tract, and the cell pattern of the peripheral blood of workers involved in manufacturing and applying DNOC [25]. In agricultural workers exposed to airborne DNOC at an average concentration of 0.0007 mg/liter (0.7 mg/cu m), slight unspecified changes in the blood and in the autonomic nervous system were observed [25]. Although the author did not describe the changes in detail, the airborne

DNOC levels in this report were the lowest found in the literature that were associated with health effects in humans.

Another study [27] revealed that agricultural sprayers had an average respiratory exposure to DNOC of 0.4 mg/hour. If one assumes the workers' average minute volume was 28.6 liters of air/minute (average minute volume for a man doing light work [28]), then their respiratory exposures would correspond to an airborne DNOC concentration of about 0.23 mg/cu m. This exposure had no adverse effects on the workers. They exhibited no symptoms of poisoning and their blood DNOC levels were well below those associated with toxic effects. However, since the workers were only exposed for 5 days, the effects from long-term exposure cannot be determined.

Inhalation studies in cats showed that similar concentrations of airborne DNOC were more toxic when given repeatedly than after a single exposure [25]. No effects were observed in cats exposed at 0.4 mg/cu m or 1.4 mg/cu m for 4 hours. In comparison, cats exposed at 0.2 mg/cu m for 2 or 3 months had slightly increased body temperatures and leukocyte counts and decreased hemoglobin concentrations, erythrocyte counts, and catalase and peroxidase activities. These changes, which were characterized as slight and transient, occurred after 1-2 weeks, but further exposure produced no additional effects. Two of three cats exposed at a concentration of 2 mg/cu m died. Since DNOC accumulated in the blood in humans and appeared to be excreted more slowly by humans than by cats [19,33], the increased hazard from long-term exposure observed in cats might also be expected in DNOC workers.

Since only slight effects were seen in workers exposed to DNOC at an average concentration as low as 0.7 mg/cu m for an unspecified duration,

and since short-term exposure at 0.2 mg/cu m had no lasting effect on cats, NIOSH recommends that the current Federal workplace environmental limit of 0.2 mg/cu m be retained.

(b) Sampling and Analysis

NIOSH recommends that sampling and analysis of DNOC be accomplished by the procedures outlined in Appendices I and II or by any other methods shown to be at least equivalent or superior in precision, accuracy, and sensitivity.

(c) Medical Surveillance and Recordkeeping

(1) Biologic Monitoring

Several investigators have studied the relationship between blood DNOC levels and adverse health effects [13,17,20,22] and have recommended the routine use of biologic monitoring to protect workers' health.

Harvey et al [13] gave five male volunteers 75 mg of pure DNOC orally for 5 consecutive days and demonstrated that DNOC accumulated in the blood and was eliminated from the body slowly, and that blood DNOC levels were associated with signs of intoxication. The first effect associated with overexposure to DNOC, an exaggerated feeling of well-being, was observed when the concentration of DNOC in the blood of exposed men was about 20 μg/g [17]. Headache, lassitude, and malaise developed when blood levels were greater than 40 μg/g. After almost 6 weeks, DNOC was still detected in the blood of four volunteers at about 1 μg/g. Another study [21] also showed that DNOC was eliminated slowly from humans. It took up to 8 weeks to be cleared from the serum.

A survey of cereal-crop sprayers revealed that only those with blood DNOC levels greater than 40 μg/g were adversely affected [17]. The BMR and the concentration of DNOC in the blood were measured in one of these workers [19]. On the 1st day of hospitalization, the blood DNOC level was 60 μg/g, and it was 4 μg/g 1 month later. As the blood level declined, the BMR decreased and symptoms subsided. When the blood DNOC concentration was below 20 μg/g, most symptoms had disappeared, although the man still had an elevated BMR.

Blood DNOC levels were determined in 45 of 47 women who were hospitalized after working in a field sprayed with DNOC [20]. In the women considered to be moderately or severely poisoned, blood DNOC levels ranged from 20 to 55 μg/ml. In contrast, the women who were mildly affected had blood DNOC concentrations that ranged from 7 to 37 μg/ml.

The serum levels of DNOC in 27 workers involved in the manufacture of DNOC ranged from 1.0 to 8.73 μg/ml 24 hours after their last exposure [22]. The authors reported that no signs or symptoms of poisoning were observed in the workers, although 3 did complain of excessive sweating, 1 suffered from diarrhea, and 16 had yellow skin.

The data on blood DNOC levels and effects, which are summarized in Table III-2, show that many people began experiencing signs and symptoms of toxicity when blood DNOC levels were 20 μg/g or greater and that all those with levels greater than 40 μg/g developed toxic effects. Some individual variation was observed, especially at low blood DNOC levels, but the overall data indicate that as DNOC begins to accumulate in the blood at levels greater than 20 μg/g, the likelihood that adverse systemic effects will develop becomes great.

Because of the fairly well demonstrated association between blood DNOC levels and the signs and symptoms of poisoning [13,17,19-21], NIOSH recommends that a biologic surveillance program be implemented. Exposure to DNOC during its manufacture and formulation can be controlled by instituting proper engineering controls and establishing good work practices. In these operations, the likelihood of overexposure to DNOC is not sufficient to warrant the establishment of a mandatory biologic monitoring program involving the routine determination of DNOC in blood. The benefits of such a program to the worker in manufacturing and formulating operations, where exposure can be controlled relatively easily, is outweighed by the inconvenience inherent in weekly blood sampling. However, in agriculturally related operations, such as the mixing, loading, and spraying of DNOC, and in flagging, where the proper control procedures may be more difficult to institute and maintain, and where the very nature of the process involves spraying the material into the atmosphere, the likelihood for significant respiratory and dermal exposure is much greater. In these situations, the merits of biologic monitoring far outweigh any inconvenience caused by the necessity for routine blood sampling.

Monitoring the blood of workers engaged in agricultural operations involving DNOC will provide an added measure of protection in addition to that gained through implementation of engineering controls and work practices. Blood monitoring will enable the responsible physician to assess the worker's exposure to DNOC on a regular basis during exposure (especially during periods of continuous exposure, such as occur during the spraying season) and to take appropriate steps to prevent DNOC poisoning.

The medical surveillance program should be as follows. Blood levels of DNOC in exposed workers should be measured at least once a week from blood samples taken toward the end of a workweek. Because blood sampling within 8 hours of the last exposure has resulted in temporarily high blood DNOC measurements [13,17], which are not indicative of the worker's true body burden, blood sampling should not be conducted less than 8 hours after exposure, but should be done as soon as possible thereafter. Investigators [13,17,21] have shown that DNOC accumulates in the blood and is slowly eliminated from the body; thus, it is feasible to obtain test results that are representative of the DNOC hazard potential by taking a blood sample on Monday morning from a worker whose exposure ended on Friday afternoon. If the blood DNOC level of any worker is equal to or greater than 10 μg/g of whole blood, the "warning" level, continued work is permitted but an industrial hygiene survey should be conducted to ascertain whether prescribed control procedures are adequate and are being followed by the worker. If the blood DNOC level is 20 μg/g of whole blood or greater, the worker should be removed from further contact with DNOC until the blood level falls below 20 μg/g or the responsible physician has approved the employee's return to work. If the blood DNOC level is between 10 and 20 μg/g of whole blood, continued work is permitted, but an industrial hygiene survey should be conducted to ascertain whether the prescribed procedures are adequate and are being followed by the worker. Because some symptoms of toxicity have been reported in workers with blood levels below 20 μg/g of whole blood [22,23], it is important to maintain observation of workers for signs and symptoms, regardless of the blood DNOC levels.

Any worker who exhibits an array of signs or symptoms consistent with DNOC poisoning should be immediately removed from further exposure to DNOC and placed under medical surveillance. If the blood DNOC level is 20 μg/g of whole blood or greater, further contact with DNOC should be prohibited until the blood level falls below 20 μg/g or the responsible physician has approved the employee's return to work. If signs and symptoms have subsided and the blood DNOC level is below 20 μg/g of whole blood, further work may be permitted.

NIOSH recommends that blood samples be analyzed for DNOC by the procedures outlined in Appendix III or by any other method shown to be equivalent or superior in precision, accuracy, and sensitivity.

A common sign of exposure to DNOC is a yellow coloring of the skin. Although one study [22] showed a possible relationship between DNOC serum levels and the degree of yellow staining, routine inspection of the skin is not recommended as a substitute for blood monitoring. Differentiating degrees of skin staining, as was done by Markicevic et al [22], is too arbitrary to permit development of a skin surveillance program that will assure protection of workers. However, yellow coloring of the skin probably indicates improper work practices or failure of engineering controls.

(2) Medical Examinations

Preplacement medical examinations should be made available to all persons occupationally exposed to DNOC, so that any preexisting disorders that would make employees susceptible to DNOC exposure at concentrations below the recommended limit can be identified. Employees with disorders such as cardiovascular and lung abnormalities should be

notified of their increased risk of injury and counseled by the attending physician on what measures to take. Periodic medical examinations should be made available to employees so that any adverse health effects can be detected at an early stage. The frequency of the examination should be determined by the responsible physician. Examination of the lungs, liver, kidneys, CNS, cardiovascular system, skin, and eyes should be stressed because they have been shown to be adversely affected as a result of exposure to DNOC [10-13,16,17,19-25].

(3) Medical Recordkeeping

Pertinent medical and other records, including biologic monitoring data and data of environmental exposures applicable to an employee, should be maintained for all employees exposed to DNOC and should be kept for at least 30 years after termination of employment.

(d) Personal Protective Equipment and Clothing

DNOC can be absorbed through the skin and respiratory tract [13,16,17,19-21,23]. The toxic effects that can result from inhalation of DNOC have been discussed in part (a) of this section. The effects of skin absorption of DNOC have been shown in several studies [13,16,21,23]. The evidence indicates that DNOC is slowly absorbed through the skin into the blood and can penetrate in quantities large enough to produce both local and systemic effects. Concentrations of DNOC as high as 65 μg/ml were measured in the serum of sprayers [21]. Peripheral neuritis developed in two workers dermally exposed to DNOC [23], and a child was fatally injured when DNOC was applied to his skin [16]. Therefore, protective equipment and clothing that will prevent skin contact, such as aprons, trousers, gloves, shoes, and safety goggles, should be provided. Clothing

contaminated with DNOC should be removed at the end of each workday and cleaned.

Compliance with the permissible exposure limit should protect against adverse health effects from inhalation of DNOC. However, respirators should be made available to those workers involved in operations where DNOC aerosol or vapor is present in the air in concentrations that exceed the permissible exposure limit.

(e) Informing Employees of Hazards

To reduce the likelihood of occupational injury, employers should inform all workers assigned to areas where DNOC is present of the hazards of exposure to that compound. At the start of their employment, workers should be informed about the signs and symptoms associated with overexposure to DNOC, the cumulative nature of DNOC, and the importance of removal from exposure should any signs or symptoms of poisoning develop. One of the first symptoms of DNOC intoxication is an exaggerated feeling of well-being [13,17]. Employees should be made aware of this effect and be encouraged to see medical personnel immediately despite their probable hesitancy to do so. Because many symptoms related to DNOC exposure are similar to, and easily confused with, those caused by working in warm environments, workers should be instructed to see trained personnel when these symptoms develop to determine whether they are related to the environmental temperature or to DNOC exposure. Employees should be apprised of the necessity for blood monitoring and its relation to prevention of illness. There should be a program of continuing education to keep workers up to date on information pertaining to the hazards of DNOC and to the safe handling of DNOC.

(f) Work Practices

Work practices that will prevent inhalation, ingestion, and skin contact with DNOC should be implemented because of the known hazards of exposure by these routes [6,8,10-12,14,17,19-24]. The toxic effects of inhalation and skin contact with DNOC have been discussed in parts (a) and (b) of this section, and recommendations have been made that should protect worker health. Protective clothing and equipment that will prevent contact with DNOC should be provided. In manufacturing and formulating areas there should be adequate ventilation to ensure that airborne DNOC levels remain below the permissible exposure limit. Processes should be enclosed whenever feasible to reduce the likelihood of exposure. Work practices and control measures used in agricultural spraying that would minimize or prevent exposure include the use of enclosed, temperature-controlled vehicles, the use of full-body suits with either supplied-air respirators or self-contained breathing apparatus operated in the positive pressure mode, and working upwind of all sprays and dusts whenever feasible.

Reports also indicate that DNOC is absorbed through the gastrointestinal tract and can produce systemic effects [9-14]. Two suicides were described in which DNOC was ingested by the victims, 50 g by one and 140 g by the other [14]. The effects on volunteers given DNOC orally and on patients taking DNOC orally to lose weight included the signs and symptoms of poisoning associated with increased metabolism, as well as cataracts and blindness [9-13]. Therefore, work practices should be implemented that will reduce the likelihood of ingestion. Smoking, eating, and drinking should be prohibited in areas where occupational exposure to DNOC is possible.

Spills of DNOC should be cleaned up immediately by trained personnel wearing adequate protective equipment and clothing. Easily accessible safety showers and eyewash fountains should be available in areas where DNOC is manufactured or formulated, for use in the event that exposure occurs. For DNOC applicators, adequate supplies of water in closed containers at readily accessible sites should be provided.

DNOC is a combustible solid, and its dust can be explosive in air [4]. Therefore, all sources of ignition should be controlled in areas where DNOC is used, handled, or stored.

(g) Monitoring and Recordkeeping Requirements

Industrial hygiene surveys should be conducted as soon as practicable after the promulgation of a standard based on these recommendations and within 30 days of any process change.

If the concentration of airborne DNOC in a work area exceeds the action level, personal monitoring should be performed every 3 months to ensure the adequacy of control procedures. If the concentration exceeds the recommended workplace environmental limit, personal monitoring should be performed at least weekly. Such monitoring should continue until two consecutive determinations, at least 1 week apart, indicate that workplace air levels no longer exceed the recommended limit. Monitoring every 3 months should then be resumed.

Records of environmental measurements should be retained for at least 30 years after the last occupational exposure to DNOC to permit correlation with any chronic health effects that may ensue.

# VII. RESEARCH NEEDS

Although its use in the United States is declining, DNOC still finds application in agriculture in the management of some crops. Deficiencies in the information available on DNOC were identified during the development of this document, and research in the following areas is recommended to improve protection of potentially exposed workers.

Research is needed to ascertain the health effects of long-term exposure to airborne DNOC and the concentrations at which airborne DNOC causes intoxication. If an adequate worker population is available, an epidemiologic study would be useful in investigating such effects. The effects of DNOC on organ systems and on behavior and its carcinogenic potential should be investigated. The primary consequences of DNOC exposure are its striking effect on the metabolic rate and the signs and symptoms that accompany such a change [13,17,19,20-23]. A long-term study would help to determine whether there are other adverse effects.

Several reports have indicated a correlation between DNOC blood levels and toxic effects [13,17,19,20,22]. A well-designed study, epidemiologic or other, of workers could also examine the relationship between DNOC levels in air and blood. Although there are indications that urinary DNOC levels do not correlate with health effects or blood DNOC levels, additional work in this area is needed, since urinary monitoring would be a more desirable program than blood monitoring. An appropriate investigation would be to determine whether routine measurement of urine levels of DNOC or of a particular metabolite would permit detection of the

earliest effects of DNOC exposure, so that precautionary steps could be taken at an early enough stage to prevent intoxication.

Further experiments on animals examining the full range of biologic effects produced by long-term inhalation of low concentrations of DNOC are recommended. Attempts should be made to define more clearly the consequences of DNOC exposure on the CNS, liver, kidneys, skin, and eyes, since there are indications that they can all be adversely affected.

One study on rats has suggested possible reproductive effects from DNOC exposure [37]. Further research is needed to clarify the observed effects, so that possible extrapolation to humans can be evaluated. Additional investigations of the carcinogenic, mutagenic, and teratogenic potentials of DNOC are also desirable.

Studies are needed to improve the accuracy, sensitivity, and precision of the recommended sampling and analytical methods. Further research on potential air sampling methods is particularly encouraged because the recommended technique has not been sufficiently tested.

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# IX. APPENDIX I

## METHOD FOR SAMPLING DINITRO-ORTHO-CRESOL IN AIR

This sampling method is adapted from Method No. S166 of NIOSH Analytical Methods [50].

### General Requirements

(a) Collect air samples in the breathing zones of workers to characterize the exposure from each job or specific operation in each work area.

(b) Collect samples representative of exposures of individual workers.

(c) Record the following:

(1) Date and time of sample collection.

(2) Sampling rate and duration and total sample volume.

(3) Location of sampling.

(4) Temperature, pressure, and relative humidity at time of sampling.

(5) Other pertinent information.

### Sampling

(a) Collect samples in the breathing zones of workers without interfering with their freedom of movement.

(b) Collect enough samples to permit calculation of TWA concentrations to evaluate the exposure of each worker at every operation or location in which there may be occupational exposure to DNOC.

(c) Use the following apparatus for sampling:

(1) Filter: Glass-fiber filter mounted in a filter holder and attachable to the inlet of a midget bubbler.

(2) Bubbler: Midget bubbler containing 10 ml of 0.1 M sodium hydroxide. Care should be taken to ensure that the bubbler is kept in a vertical position during sampling.

(3) Battery-operated personal sampling pump attachable to the workers' clothing, whose flowrate can be determined with an accuracy of at least 5%.

Calibration of Equipment

Since the accuracy of an analysis can be no greater than the accuracy with which the volume of air is measured, the accurate calibration of a sampling pump is essential. The frequency of calibration required depends upon the use, care, and handling to which the pump is subjected. Pumps should be calibrated if they have been abused or if they have just been repaired or received from the manufacturer. Maintenance and calibration should be performed on a routine schedule, and records of these should be maintained.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration depends on the type

of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, a spirometer or soapbubble meter is recommended, although other calibration instruments, such as a wet test meter or dry gas meter, can be used. The actual setups will be similar for all instruments.

The calibration setup for a personal sampling pump with a glass-fiber filter and midget bubbler is shown in Figure XIII-2. Since the flowrate given by a pump depends on the pressure drop across the sampling device, in this case a glass-fiber filter and midget bubbler, the pump must be calibrated while operating with a representative glass-fiber filter and midget bubbler in line. Instructions for calibration with the soapbubble meter follow. If another calibration device is selected equivalent procedures should be used.

(a) Check the voltage of the pump battery with a voltmeter to ensure adequate voltage for calibration. Charge the battery if necessary.

(b) Assemble the sampling train as shown in Figure XIII-2.

(c) Turn on the pump and moisten the inside of the soapbubble meter by immersing the buret in the soap solution and drawing bubbles up the inside until they are able to travel the entire length of the buret without bursting.

(d) Adjust the pump flow controller to provide the desired flowrate.

(e) Start a soapbubble up the buret and measure with a stopwatch the time the bubble takes to move from one calibration mark to another.

(f) Repeat the procedure in (e) at least three times, average the results, and calculate the flowrate by dividing the volume between the

preselected marks by the time required for the soapbubble to traverse the distance. If, for the pump being calibrated, the volume of air sampled is the product obtained by multiplying the number of strokes times a stroke factor (given in units of volume/stroke), the stroke factor is the quotient obtained by dividing the volume between the two preselected marks by the number of strokes.

(g) Data for the calibration include volume measured, elapsed time or number of strokes, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and the name of the person performing the calibration.

Collection and Handling of Samples

(a) Place the filter and bubbler so that the sampled air passes first through the filter and then through the bubbler.

(b) Sample at a flowrate of 1.5 liters/minute. A sample size of 120 liters is recommended.

(c) Immediately after sampling, seal the filter container and remove and clean the bubbler stem. Wash the stem with 1-2 ml of the collecting medium. Include the wash solution in the bubbler and record the amount used. Seal the top of the bubbler tightly with a plastic stopper and place the bubbler upright in a carrying case. Care should be taken to minimize spillage or loss by evaporation at all times.

(d) Treat at least one filter and one bubbler in the same manner as those in the sample train, but do not draw air through them. These will serve as blanks.

# X. APPENDIX II

## ANALYTICAL METHOD FOR DINITRO-ORTHO-CRESOL

This analytical method is adapted from NIOSH Method No. S166 [50].

### Principle of the Method

(a) A known volume of air is drawn through a glass-fiber filter followed by a midget bubbler to collect DNOC particulate and vapor.

(b) The filter is extracted with 0.1 M sodium hydroxide, and the extract is analyzed with the sample collected in the midget bubbler.

(c) DNOC is measured directly in this solution with a spectrophotometer at 395 nm.

### Range and Sensitivity

The method has been tested for a 120-liter sample of air over a range of 0.0821-0.295 mg/cu m.

### Interferences

No information is available on the possible sources of interferences in the sampling and analytical methods discussed.

Precision and Accuracy

The mean coefficient of variation for the sampling and analytical method in the range of 0.0821-0.295 mg/cu m was 0.154. This value corresponds to a standard deviation of 0.03 mg/cu m at the 0.2 mg/cu m level.

Advantages of the Method

(a) The sampling device is small, portable, and suitable for determining DNOC in both the particulate and vapor forms.

(b) The analysis is accomplished by means of a quick instrumental method.

Disadvantages of the Method

The sampling device requires the use of liquid in bubblers that can pose problems in field measurements because breathing-zone samples are difficult to collect and to transport without spillage.

Apparatus

(a) Spectrophotometer, visible range.

(b) Volumetric flasks: convenient sizes for making dilutions and standard solutions.

(c) Cuvettes: 5-cm cells.

Reagents

(a) DNOC, spectrograde (the specific isomer to use will depend on which one is used in the workplace).

(b) Sodium hydroxide, 0.1 M.

(c) Acetone.

Preparation of Calibration Curve

(a) Prepare a standard solution containing 3.0 $\mu g/\mu l$ DNOC in acetone.

(b) Place measured amounts, 2-40 $\mu l$, of this standard DNOC solution in 25 ml volumetric flasks containing 10 ml of 0.1 M sodium hydroxide.

(c) Dilute to 25 ml with 0.1 M sodium hydroxide.

(d) Prepare a blank consisting of 25 ml of 0.1 M sodium hydroxide with 8 $\mu l$ of acetone.

(e) Measure the absorbance of each standard solution at 395 nm in 5-cm cells against the blank.

(f) Plot absorbance readings against $\mu g$ of DNOC.

Analytical Procedure

(a) Preparation of Sample

Analyze the samples from the glass-fiber filter and midget bubbler together. Extract the filter with 0.1 M sodium hydroxide and combine the extract with the contents of the midget bubbler.

(b) Measurement of DNOC

(1) Dilute sample to 25 ml with 0.1 M sodium hydroxide.

(2) Transfer sample to a 5-cm cell. Read absorbance at 395 nm against a blank.

(3) Convert the corrected absorbance to micrograms of DNOC by means of the calibration curve.

Calculations

The concentration of DNOC in air can be expressed as milligrams of DNOC/cubic meter of air, which is numerically equal to micrograms of DNOC/liter of air:

$$\text{mg DNOC/cu m} = \mu\text{g DNOC}/V$$

where:

$\mu$g DNOC = micrograms of DNOC from the calibration curve
$V$ = volume of air sampled (in liters) at 25 C and 760 mmHg

# XI. APPENDIX III

## ANALYTICAL METHOD FOR DINITRO-ORTHO-CRESOL IN THE BLOOD

This analytical method is based on methods described by Parker [52] and Fenwick and Parker [53].

### Principle of the Method

Whole anticoagulated blood is extracted with methyl ethyl ketone (MEK) in the presence of sodium chloride and sodium carbonate. The absorbance of the yellow extract is measured before and after addition of acid at 430 nm against an MEK blank. Concentrations of DNOC in blood are calculated using a standard curve prepared with DNOC.

### Range and Sensitivity

The range of the method is 5 to 50 $\mu$g/g blood using the dilutions described below. The author reports a sensitivity of 0.5$\mu$g/ml.

### Interferences

This procedure measures MEK extractable yellow pigments. Interferences from yellow blood pigments such as beta-carotene and bilirubin are minimized by use of a blank. Possibilities for false positives exist only under marked abnormally high bilirubin or carotene blood concentrations.

Advantages and Disadvantages

The procedure is a simple, direct method for determining blood DNOC concentrations; however, it is not specific. It is known that 2,4-dinitrophenol reacts. The procedure is also subject to interference from abnormally high concentrations of beta-carotene and bilirubin in the blood.

Apparatus

(a) Spectrophotometer, 20 nm band pass, equipped for round cuvettes.

(b) Tabletop centrifuge culture tubes, 12 x 125 nm, with Teflon-lined caps (for extraction).

(c) Matched set of round cuvettes.

(d) Trip balance.

(e) Analytical balance.

(f) Hot plate.

(g) Round bottom flask, 250 ml, attached to a condenser.

(h) Beaker, 1 liter.

(i) Volumetric pipets, assorted sizes.

(j) Volumetric flasks for standards.

(k) Rubber suction bulb.

(l) Disposable transfer pipets.

(m) Fume hood.

(n) Test tubes, 13 x 100 mm.

Reagents

All reagents shall be ACS reagent grade or equivalent.

(a) Methyl ethyl ketone (2-butanone).

(b) Sodium chloride-sodium carbonate: Mix 1 part anhydrous sodium chloride with 9 parts anhydrous sodium carbonate.

(c) Concentrated hydrochloric acid.

(d) DNOC: 4,6-dinitro-o-cresol (IUPAC); 3,5-dinitro-o-cresol (common name).

Procedure

(a) Cleaning of Equipment

Glassware should be cleaned with detergent and rinsed with distilled water.

(b) Collection and Shipment of Samples

Venous blood should be collected without stasis in a 5-7 ml vacuum blood collecting tube containing EDTA anticoagulent. Blood tubes shall be inverted 10-20 times immediately after collection to insure mixing of blood and EDTA. Blood samples should be maintained at 4 C until analysis. Avoid freezing. Blood samples can be conveniently shipped in styrofoam cartons containing bagged "camp ice." Blood samples should be stable up to 7 days at 4 C.

(c) Analysis of Samples

(1) Weigh out 1.0 g of well-mixed whole blood in each of two extraction tubes. Label the tubes "test" and "blank." Five ml of MEK is added to each tube, and the tubes are capped and gently shaken to

disperse the blood. (Caution: Use a fume hood and avoid breathing MEK vapors.)

(2) One to two (1-2) grams of the sodium chloride-sodium carbonate mixture is added to each tube, and the tubes are capped and vigorously shaken for 30 seconds. The tubes are centrifuged briefly (1 minute), and the upper MEK layer is transferred to marked test tubes. To the tube marked "blank," add one drop of concentrated hydrochloric acid and centrifuge for 1 minute to remove cloudiness. Transfer the contents of both tubes to match cuvettes and read the absorbance at 430 nm, setting the spectrophotometer to zero with an MEK blank. Subtract the "blank" reading from the "test" reading, and determine the concentration of DNOC in blood by reference to a standard curve. If the absorbance of the "blank" exceeds 0.15, interference from blood pigments can be suspected.

Preparation of the Standard Curve

One hundred (100) milligrams of free DNOC and 100 ml of a 0.5% (w/v) sodium carbonate solution are placed in a 250-ml round-bottom flask equipped with a condenser. Heat the mixture on a boiling water bath (hot plate and 1 liter beaker with water) until the DNOC is dissolved. (Note that the boiling point of DNOC is 85-86 C and that a condenser is needed to avoid loss of DNOC.) Cool, rinse the condenser with 0.5% sodium carbonate solution, transfer the DNOC solution and the rinse to a 250-ml volumetric flask, and make up to volume with distilled water. This is the stock standard at 400 μg DNOC/ml. Prepare working dilutions with distilled water from 5-50 μg/ml. The standard curve is prepared by extracting 1.0-ml

portions of the diluted standards exactly as described above for blood. Plot the absorbance vs the concentration of DNOC in μg.

Calculations

The absorbance of the blood ("test" - "blank") is compared with the standard curve. The μg DNOC then is a direct measure of DNOC in μg/g blood if 1.0 g blood was used.

## XII. APPENDIX IV

## MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity

or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments for DNOC might be:

> Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possible irritation, skin staining and local and systemic effects.
>
> Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill," or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

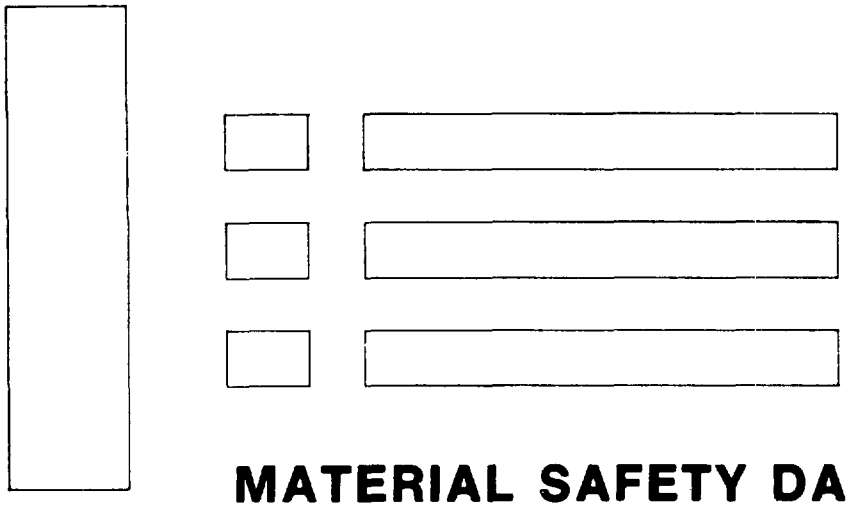
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



# MATERIAL SAFETY DATA SHEET

| I PRODUCT IDENTIFICATION | |
|---|---|
| MANUFACTURER'S NAME | REGULAR TELEPHONE NO<br>EMERGENCY TELEPHONE NO |
| ADDRESS | |
| **TRADE NAME** | |
| **SYNONYMS** | |

| II HAZARDOUS INGREDIENTS | | |
|---|---|---|
| MATERIAL OR COMPONENT | % | HAZARD DATA |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

| III PHYSICAL DATA | | | |
|---|---|---|---|
| BOILING POINT, 760 MM HG | | MELTING POINT | |
| SPECIFIC GRAVITY ($H_2O$=1) | | VAPOR PRESSURE | |
| VAPOR DENSITY (AIR=1) | | SOLUBILITY IN $H_2O$, % BY WT | |
| % VOLATILES BY VOL | | EVAPORATION RATE (BUTYL ACETATE 1) | |
| APPEARANCE AND ODOR | | | |

## IV FIRE AND EXPLOSION DATA

| | | | |
|---|---|---|---|
| FLASH POINT (TEST METHOD) | | AUTOIGNITION TEMPERATURE | |
| FLAMMABLE LIMITS IN AIR, % BY VOL. | LOWER | | UPPER |
| EXTINGUISHING MEDIA | | | |
| SPECIAL FIRE FIGHTING PROCEDURES | | | |
| UNUSUAL FIRE AND EXPLOSION HAZARD | | | |

## V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

## VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

## VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

## VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

## IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS _____

DATE _____

## XIII. TABLE AND FIGURES

### TABLE XIII-1

### PHYSICAL AND CHEMICAL PROPERTIES OF 4,6-DINITRO-o-CRESOL

| | |
|---|---|
| Molecular formula | C6H2(CH3)OH(NO2)2 |
| Formula weight | 198.13 |
| Appearance | Yellow solid |
| Melting point | 85.8 C |
| Vapor pressure | 0.000052 mmHg at 20 C |
| Saturated concentration (at 20 C) | 0.56 mg/cu m<br>(0.068 ppm) |
| Specific gravity | - |
| Solubility | 0.01 % by weight in water at 20 C<br>1.82 in alcohol at 15 C |
| Minimum cloud ignition temperature | 340 C |
| Minimum explosive dust concentration | 0.03 g/liter<br>(30 g/cu m) |
| Vapor density (air = 1) | 6.8 |
| Conversion factors (760 mmHg and 20 C) | 1 mg/cu m=0.12 ppm<br>1 ppm=8.2 mg/cu m |

Adapted from references 2-4

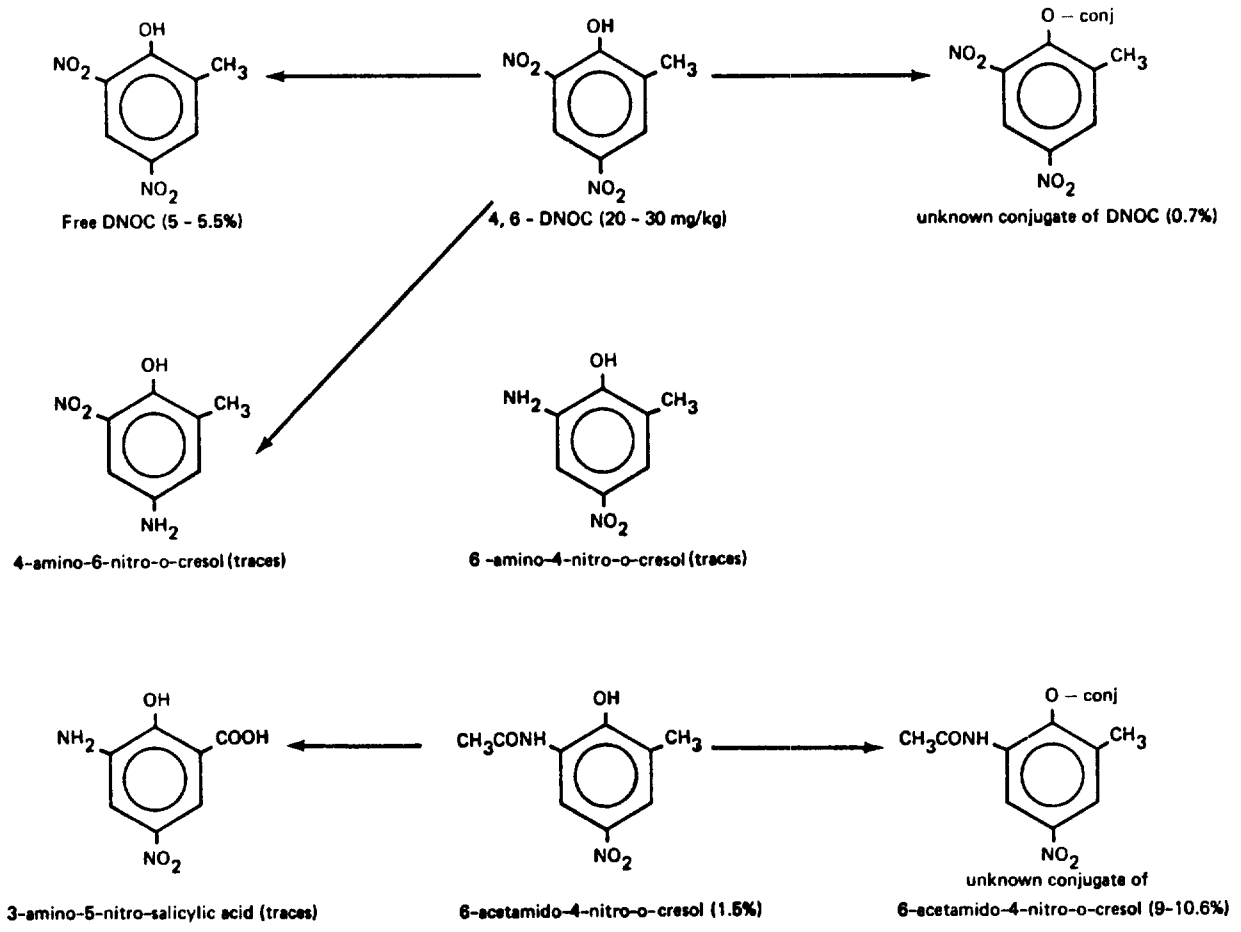



FIGURE XIII-1

METABOLIC PATHWAYS OF 4,6-DINITRO-o-CRESOL
ADMINISTERED BY STOMACH TUBE TO RABBITS

Adapted from Smith et al [46]

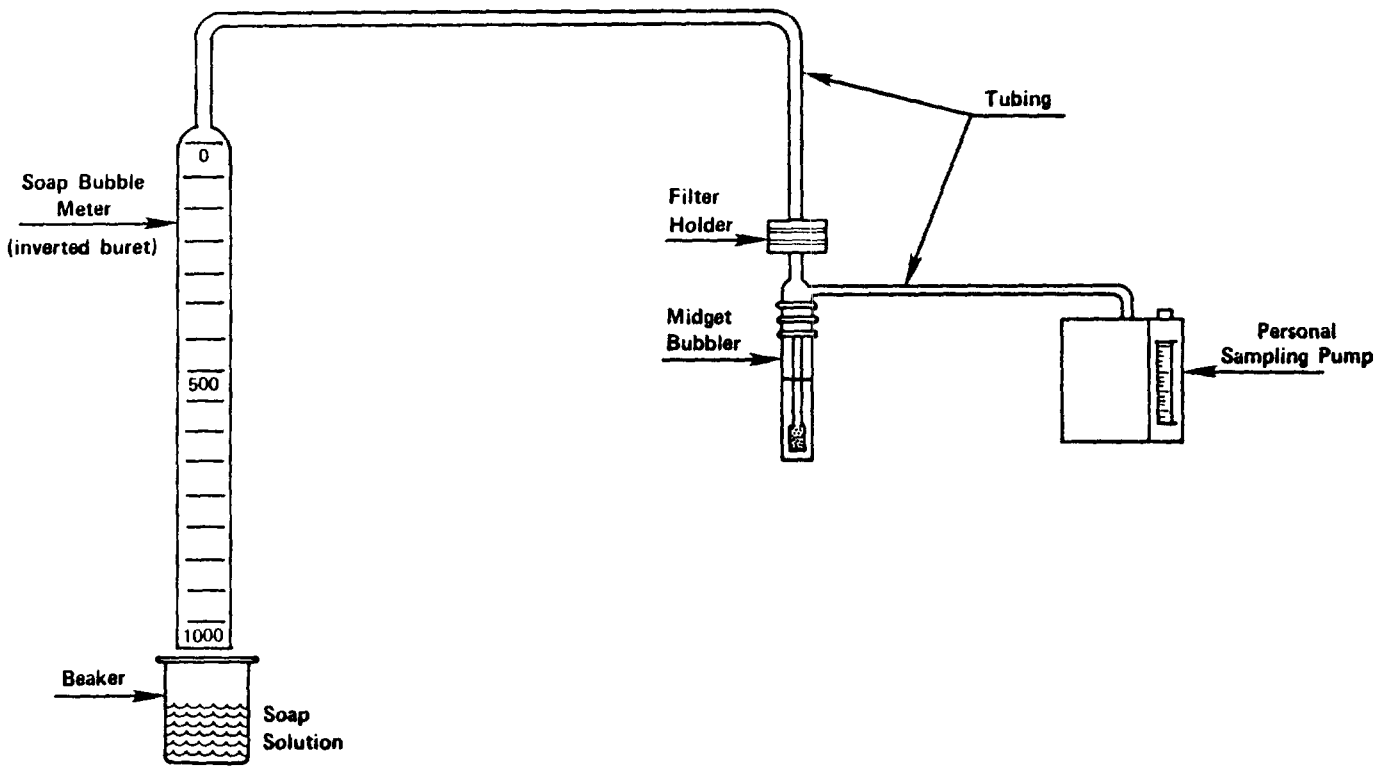



FIGURE XIII-2

CALIBRATION SETUP FOR PERSONAL SAMPLING
PUMP WITH FILTER HOLDER AND MIDGET BUBBLER



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