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 $\mu g/g$ of whole blood or greater, further contact with DNOC should be prohibited until the blood level falls below 20 $\mu g/g$ 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 $\mu g/g$ 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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