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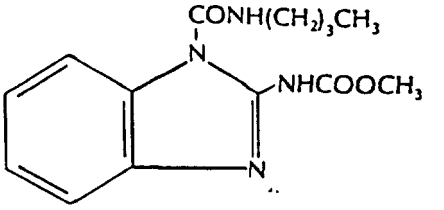
BENOMYL

Methyl **1-(butylcarbamoyl)-2-benzimidazolecarbamate; Benlate**



$C_{14}H_{18}N_4O_3$

TLV, 10 mg/m³

STEL, **15 mg/m³**

Benomyl is a white crystalline solid, which has a molecular weight of **290.32.** *It* decomposes without melting and has a negligible vapor pressure, indicating exposure would be in particulate form. Very slightly soluble in water, it is soluble in xylene, acetone, *dimethylformamide* and chloroform.(') Fluorometric and *colorimetric*[2] *and* liquid *chromatographic*[3] procedures for determining residues of benomyl have been published.

Benomyl is the common name for this fungicide and ascaricide.

The acute oral LD_{50} for the rate is $\geq$10,000 mg/kg. The acute skin absorption LD_{50} for the rabbit is $\geq$10,000 mg/kg. Application to the shaved intact skin of ten male guinea pigs, at each level as aqueous suspensions containing *5,* **12.5** and 25% benomyl as the active ingredient in a *50%* wettable powder, resulted in negligible irritation. One of ten guinea pigs had mild erythema two days after application at the high rate. All guinea pigs at the two lower rates and in a control showed no irritation after two days.[4] Instillation into the eyes of rabbits of 10 mg of dry 50% powder or 01 mL of 10%suspension in mineral oil caused only temporary mild conjunctival irritation.[1] The acute inhalation LC_{50} is $\geq$2000 mg/m³ ($\geq$ 2 mg/L) for rat[1] and is equivalent to $\geq$825 mg/m³ ($\geq$ 0.825 mg/L) for dog[4] for four-hour exposures. Histologically, there was reduction of spermatogenic activity in some animals. With regard to this activity, no-effect levels for benomyl for four-hour exposures are equivalent to $\geq$100 $\leq$410 mg/m³ ($>$ 0.1 $\leq$0.41 mg/L) for the rat and $\geq$325 $\leq$825 mg/m³ ($\geq$ **0.325** $\leq$0.825 mg/L) for the dog. Additionally fifteen four-hour inhalation exposures at the equivalent of 100 mg/m³ (0.1 mg/L) of benomyl over a period of three weeks produced no clinical or histopathologic indication of accumulative effects in the rat.[4]

A low order of toxicity has been found in chronic studies. In two-year feeding studies no-effect levels in the diet are **2500** ppm (0.25%) for rats (highest level fed) and 500 ppm (0.05%) for dogs. Pesticide residue tolerances have been established in many food crops. They are as high as 15 ppm for stone fruits and food additive tolerances are as high as *50* ppm for raisins.[1] In a three-generation rat reproduction study no compound-related reproduction or lactation differences were observed among control and test groups even at 2500 ppm (0.25%), the highest dietary level fed. In a teratogenic study in rat neither the outcome of pregnancy nor embryonal development was affected even at 5000 ppm (0.50%), the highest dietary level fed. In a dominant lethal mutagenic study in the rat, benomyl was not mulagenic at 2500 ppm (0.25%), the highest dietary level fed.[5]

Cardiner *et al*[6] showed that rat and dog eliminated $\geq$99% of single, oral doses of 2-^{14}C benomyl via the urine and feces within 72 hours. The major metabolite was methyl 5-hydroxy-2-benzimidazole-carbamate which was present in the urine as glucuronide and/or sulfate conjugates. Residue data on dog and rat tissues from two-year chronic feeding studies demonstrated that benomyl and its metabolites do not accumulate in animal tissues.

In view of the low order of acute and chronic toxicity the TLV of 10 mg/m³ and the STEL of 15 mg/m³ appear appropriate.

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BENZENE

C_6H_6

TLV, 10 ppm ($\approx$ **30 mg/m³),** Appendix A2 — Suspected Carcinogen

STEL, 25 ppm ($\approx$ 75 mg/m³), Appendix A2

Benzene is a colorless, non-polar liquid, with an odor characteristic of aromatic hydrocarbons. It has a molecular weight of 78.11, a boiling point of 80.1° C, a melting point of 5.5° C, a vapor pressure of 75 mm Hg at 20° C and a specific gravity of 0.87865 at the same temperature. Benzene has a flash point of –11.1° C (closed cup, 12° F), making it a dangerous fire hazard. It was formerly derived almost exclusively by distillation of coal tar, but now comes primarily from petroleum, either by extruction or by dealkylation of toluene. Benzene is slightly soluble in water, but soluble in all proportions in alcohol, acetone and ether.

At one time benzene was an important solvent, especially for rubber, as a diluent in lacquers, and in paint removers. At present such uses are minimal; most benzene consumed in the chemical industry, as a raw material to

numerous organic chemicals. It is found in gasoline from trace amounts to as much as 30% concentration in some countries.

As an acute poison benzene produces narcotic effects comparable to those of toluene; it is a more potent narcotic than the alkanes or naphthenes of similar boiling points. But the effect of chronic exposure to this compound is by far the most serious disease caused by any of the common hydrocarbon solvents. Its action on the bone marrow may result in detectable alterations, and, in some instances, aplastic anemia. Xhe reported LD_{50} orally in young adult rats is 3.8mL/kg.[1]

It is unique among hydrocarbons as a myelotoxicant.[2] More than 140 fatal cases of benzene poisoning had been recorded prior to 1959.[3] Vigliani and Saita[4] listed *26* deaths from chronic benzene poisoning in two provinces in Italy between 1960 and 1963. Eleven of these were diagnosed as leukemia, which may develop several years after cessation of exposure to benzene.

Most deaths from benzene have resulted from exposures of the order of 200 ppm or more. In a few instances concentrations of 1000 or even 2000 ppm have been recorded in workplaces where deaths occurred. Some of these are: Legge,[5] 210 to 1050 pprn: Greenburg,[6] 70 to 1800 ppm, with over half above 200; Bowditch,[7] 100 to 200+ measured; one leukemia case described by Hunter[8] and Mallory[9] six years after exposure at over 200 ppm; Greenburg,[10] 25 to 1000 pprn in four rooms; Helmer,[11] 140 to *200* ppm after improvements; Savilahti,[12] 318, 433 and 470 ppm; Kozlova,[13] 47 to 310 ppm; Vigliani,[4] 190 to 660 pprn, after four years death from leukemia; Juzwiak,[14] 31 to 156 pprn; Aksoy,[15] 150 to *650* ppm, and 210 to 650 ppm,[16] 26 patients with acute leukemia or preleukemia; Ikeda,[17] 100 to 800 ppm, 7 deaths, all females, none from leukemia.

Winslow,[18] however, reported blood changes in workers where concentrations of benzene vapor below 100 ppm were found. Heimann and Ford[19] found one death and three cases with blood changes where air analysis for benzene showed a concentration of 105 ppm. Wilson[20] reported three fatal cases in a plant where the average concentration of benzene vapor was 100 ppm. In a fifth room, associated with benzene poisoning, Greenburg[10] found 11 to 57 ppm. So far as can be determined the lowest ***measured*** concentration of benzene vapor associated with a fatal case of benzene intoxication (due to aplastic anemia) was the 60 ppm reported by Hardy and Elkins in 1948,[21] in a plant where repeated air analyses were made, and a number of other workers showed some blood abnormalities.

Blaney[22] found little evidence of benzene intoxication in a group of 90 workers regularly exposed to benzene for about 13 years. Concentrations were generally low, but urinary phenol measurements indicated some exposures of the order of 25 ppm.[23] A followup several years later showed no evidence of persisting blood dyscrasias. No cases of leukemia are known to have Occurred in this Group of workers. Pagnotto *et al*[24] found workers in rubber spreading operations involving naphtha with a relatively high benrcne content exposed to benzene in concentrations which were tor the most part between 6 and 25 ppm. A number ot blood studies showed a few abnormalities but only two were seious to warrant special consideration. In one case the possibility ot leukemia was raised, but on being removed from his job and given iron therapy the worker recovered. Because of several job changes his benzene exposure could not be reliably estimated.

The other worker was in a group studied intensively over a period of several years by Pagnotto.[25] He had a red count below four million, a hemoglobin below twelve grams and suffered from nose bleeds. His benzene exposure, as estimated from several urinary phenol determinations, was to about 40 ppm. After his exposure to benzene was terminated, his blood picture gradually returned to normal. The 38 workers in this plant were followed up for 15 years after the use of naphtha containing benzene was discontinued. None showed any signs of permanent blood abnormalities. There were three deaths, none being from leukemia. It was concluded that 25 ppm of benzene vapor is safe for most workers, but that since the margin of safety is small, a TLV of 10 ppm was recommended.[25] Elkins[26] in a summary of the findings in the rubber spreading industry, came to a similar conclusion.

These conclusions were consistent with those of Fuchs[27] in 1969, who found variations in the blood pictures of three workers but did not consider that the changes were proved to result from their benzene exposures of 19, 28 and 43 ppm, respectively. He also stated that he could find no data in the literature on proved benzene poisoning in concentrations below 16 ppm, nor could he find any Soviet report which cited reasons for decreasing the Russian MAC to *6* ppm.

Two investigators have studied the effects on rats oi exposures at relatively low levels of benzene vapor extended periods. Deichmann er *al*[28] found that after 5 to 8 weeks of 5 hour/day, 5 days/week exposure at 44 and 47 ppm, rats developed a moderate degree of leukopenia, but that none resulted from 15 to 31 ppm. Nau *et al*[29] found a decrease in the white blood cell counts of rats following 756 hours of exposure at 50 ppm of benzene on a schedule of 8 hours/day, 5 days/week. Reduced amounts of DNA in the white cells, a depression in myelocytic activity, and an increase in the relative numbers of red cell precursors in the bone marrow were also observed.

There have been numerous reviews of the literature or benzene intoxication. Noteworthy are those of the National Academy of Sciences in 1976[30] and the NIOSH criteria document on benzene. published in 1974.[31] As a result of this extremely thorough review, NIOSH recommended a workplace time weighted average standard oi 10 ppm, with a ceiling of 25 ppm.

In 1976, however, NIOSH issued a revised recommendation for an occupational exposure standard for benzene.[32] The key to this recommendation is the statement in the introduction that *"**Because** it* is *not* ***at present possible*** to ***establish a safe*** *exposure* ***level*** *tor* ***a carcinogen, the NIOSH recommendation*** *is* to ***restrict exposure*** to ***very low levels rvhich can still be reliably measured*** *in* ***the workplace."*** A number of references are given. primarily lo support the characterization of benzene as a carcinogen (leukemogen). Thus most relate lo leukemia cases associated with heavy benzene exposures, either measured or interred from association with numerous cases of aplastic anemia or other blood dyscrasias. Others are epidemiologic studies on cancer in which no evidence ot the degree, or even iact, ot benzene exposure is cited. Thus in at least two ot these papers,[33,34] the word "benzene" does not appear. In these and other papers the incidence of various types of cancer.

including leukemia, was found to be higher than in the general population among certain groups of rubber workers. Monson and Nakano[35] found 55 cases of leukemia, vs. 43 expected, among rubber workers. It was noted that benzene has been used extensively in the rubber industry, but is no longer employed, although it is a contaminant of extensively used naphtha solvents. The degree of exposure to benzene in the rubber industry during the first half of the 1940-1950 decade may well have been excessive. Wilson[20] has noted deaths and blood abnormalities among workers in the rubber industry during the war years who were exposed, on the average, to concentrations of benzene vapor of 100 ppm. Neither Monson-Nakano or other authors of similar papers quoted in the NIOSH update mention whether or not aplastic anemia or other blood dyscrasias, apart from leukemia, occurred in the groups of workers that were studied.

Nevertheless OSHA, in 1977, issued an Emergency Temporary Standard (ETS)[36] establishing a TWA limit of 1 ppm for benzene vapor. (Enforcement of this standard was voided by the courts). Much of the evidence substantiating this action was the same as that quoted in the NIOSH update. However, one additional paper was cited by Infante et *al*,[37] in which nine leukemia deaths were reported from two rubber film casting plants where benzene vapor concentrations allegedly ranged from 0 to 15 ppm. This report was critically examined in OSHA hearings on a permanent standard, with essentially the same provisions as the ETS, which were held during the summer of 1977. The data on benzene exposure in the two plants in question, especially during the first part of the ten year employment period (1940 to 1950) covered by the study, were found to be incomplete, unreliable and contradictory. Even in 1976 a NIOSH report of one of the plants involved, or its successor, showed concentrations in excess of 15 ppm at several locations.[38] A study by Harris *et al*[39] in 1973 and 1974 revealed similar findings, although the overall average of all sample results was slightly above 1 ppm. During the period 1940 to 1945 or so, when many of the involved workers were employed, the permissible concentration for benzene exposure (ASA standard) was 100 ppm. In common with the papers cited by the NIOSH update, no information on other blood abnormalities was given in the Infante report.

Epidemiologic studies of workers exposed to measured low concentrations of benzene vapor have yielded negative or inconclusive results. Thorpe[40] after studying the occurrence of leukemia in a population of 38,000 workers in a variety of European petroleum and petrochemical operations, some of whom were exposed at levels of benzene that occasionally reached *20* ppm, over a period of ten years, found that deaths from leukemia "were not abnormal" for the countries involved (18 vs. 23.23 expected).

Retrospective studies of employees of a large chemical company, exposed ior many years to benzcnc, mostly at low levels, revealed no excess mortality.[41,42] A cohort of 594 workmen were divided into four exposure groups: very low exposures, less than 2 pprn as time weighted average (TWA); low exposures, 2-9 ppm; moderate exposures, 9-24 ppm; and high exposures, above *25* ppm. In many areas there was exposure to other chemicals as well as to benzenc. The duration of exposure was also divided into four groups, with 186 workers having in excess of 20 years.

Of 102 deaths, two were due to anemia, two to leukemia, and one had leukemia as a complication. Of these five cases, only one, an autopsy-confirmed pernicious anemia, involved a previous exposure to benzene of significance, 5520 ppm months. The other anemia death, diagnosed as being of the aplastic type, was of a worker with 453 ppm months of benzene exposure. Two of the leukemia cases involved exposures of 545 and-305 ppm months, respectively, while the third was of a worker with only 18 ppm months benzene exposure.

To put these exposure data in perspective, three of the deceased workers had had exposures to benzene equivalent to 40 years' employment in concentrations slightly above or below 1 ppm; the exposure of the fourth, if spread over 30 years, would have been at a concentration of 0.05 ppm.

The predicted deaths from anemia and leukemia were 02 and 1 respectively. The fact that, apart from the pernicious anemia death, there appeared to have been no dose response relationship, apparently led to the conclusion of the authors that "*no mortality* findings directly *attributable* to benzene exposure were observed".

The NIOSH update mentions the consistent observations of chromosomal aberrations associated with benzene exposure, but further comments that the implications of these findings with respect to benzene leukemia are still not clear. The possbility of a chromosomal instability acting as a stimulus for a latent leukemogenic virus has been speculated upon.[43] This question was discussed at some length at the International Workshop on the Toxicology of Benzene, held in Paris in November 1976. Tough[44] hac previously reported that marked aberrations were founc only in plants where concentrations of benzene vapor were believed to be between 25 and 250 ppm, and that nc significant changes were observed at 12 ppm. Forni,[45] however, stated that there had been a few positive, as wel as negative, reports at levels between 5 and 25 ppm. Th consensus of opinion was that the significance of the find ing of increased chromosome aberrations for the occur rence of benzene leukemia was still not clear. Maugeri an Pollini[46] reported that among Italian shoe workers *"almos all* the cases of *haemopathy* due to benzol which lead t *death* show features *of terminal* leukemia,. ..*and (the leu* kernias) were always preceded *by* aplastic conditions".

Opinions of the workshop participants relative to th appropriate TLV for benzene were varied. The final recom mendation was to retain 10 pprn as a permissible TWA which must not be exceeded, but it was also specified tha benzene should not be employed when substitute mate rials were available.

DeGowin's report[47] of a case of leukemia following a apparent benzene-induced aplastic anemia contains a dis cussion which implies that there is evidence that aplasti anemia per se may lead to leukemia, and that delave cases of this disease are not confined to aplastic anem due to benzene.

It is the opinion of the Committee that the characteriz tion of benzene as a leukemogen, by NIOSH, is, in essens valid, although benzene may be what Truhaut has de scribed as a "secondary carcinogen".[48] An A2 notatic should be applied to benzene in the TLV listings.

On the other hand, the Committee does not agree wi the NIOSH recommendation of 1 ppm as an occupatior

exposure standard, insofar as the TLV can be defined as such a standard. There is little evidence that exposure to benzene at concentrations below 25 ppm causes blood dyscrasias of any kind. Setting the TLV at 10 ppm, as a time-weighted average, provides an added margin of safety.

If the standard is to be set at the lowest practicable detectable limit, it is the opinion of some members of the Committee that a value lower than 1 ppm should be selected. In the absence of interfering substances benzene vapor can be measured with reasonable accuracy in concentrations at least as low as 0.1 ppm; in the presence of certain interferences, it may be difficult to achieve the prescribed accuracy and reliability even at concentrations somewhat above 1 ppm.

Because the effects the TLV is designed to prevent are chronic in nature, a ceiling designation is not appropriate and a STEL of 25 ppm is recommended.

Other recommendations: ANSI (1969) 10 ppm; Czechoslovakia (1969) 16 ppm; USSR (1972)1.6 ppm; DDR (1973) 16 ppm; Sweden (1975)10 ppm; BRD (1974)0 pprn (treats as carcinogen).

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