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Hazard Review of Beta-Naphthylamine (2-NA)

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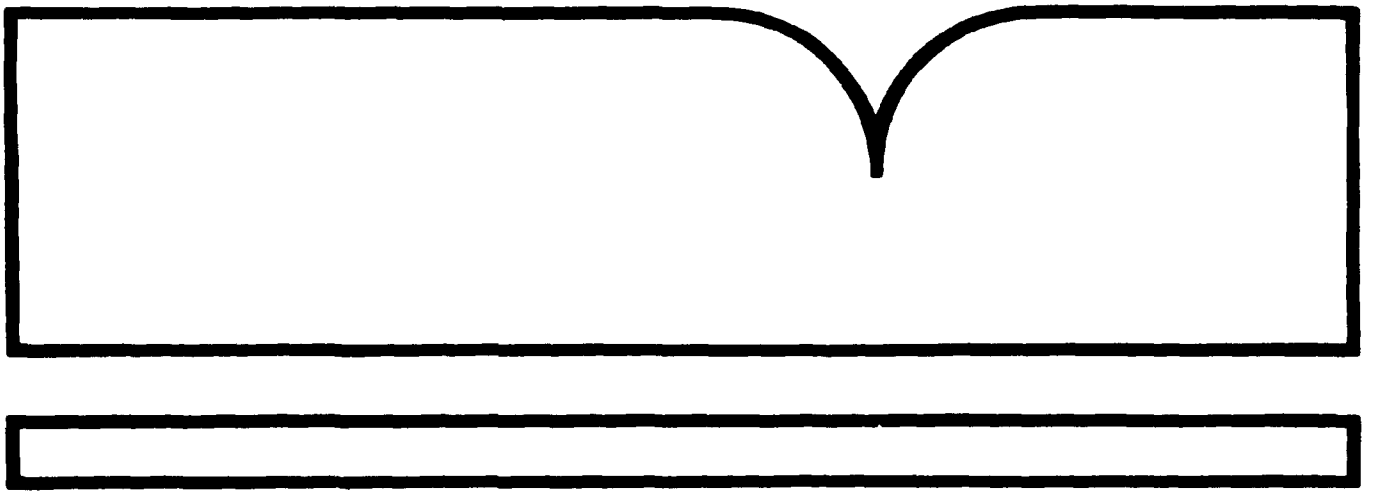

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16. Abstract (Limit: 200 words)
The hazards of occupational exposure to beta-naphthylamine are reviewed. The epidemiological pitfalls of determining carcinogenicity of the dye are outlined. These are: worker exposure to more than one suspect compound, complicated by shifting of workers between departments; different degrees of exposure hazard between processes; unsuspected impurities in trace amounts that are possibly more harmful than the parent compound; and differences in composition of dyes and production methods in different factories that complicate statistical comparisons. Animal experiments are cited in which dogs given subcutaneous injections or fed the dye developed bladder tumors. Bladder papillomas, hepatomas, bronchogenic carcinomas, and lung carcinomas produced in Wistar-rats are noted. Proof of carcinogenicity of the dye in mice, monkeys, and hamsters is also presented. Fifteen metabolites identified for beta-naphthylamine are listed. An epidemiological study is described in which 109 of 376 workers exposed to beta-naphthylamine and other aromatic amines in a dye factory had bladder malignancies. Of 54 of these workers exposed to beta-naphthylamine, 31.5 percent had bladder malignancies. The latency period ranged from 6 to 38 years; mixed exposures to beta-naphthylamine and benzidine resulted in 50 percent bladder malignancies. The author concludes that the carcinogenicity of beta-naphthylamine is well established by both animal data and human experience. It is clearly implicated as a highly hazardous substance in occupational environments.

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HAZARD REVIEW

OF

BETA-NAPHTHYLAMINE (2-NA)

July 1973

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Hazard Review

of

beta-Naphthylamine (2-NA)

(2-Naphthylamine)

Occupational exposure to aromatic amines has long been associated with development of bladder cancer. Historically, the population-at-risk has been limited to individuals employed in the "aniline" dye industry. The term, "aniline cancer" was used in earlier days to denote cancer of the urinary bladder in workers engaged in the production of "aniline" dyes. Hueper [1] published a paper in 1934 in which he reviewed the history, significance, and epidemiologic evidence of "aniline cancer" in the dye industry. Hueper credited Rehn with reporting the first cases of occupational bladder tumors in 1895 in three workers in a German dye factory. In his review article Hueper mentioned the beginning of what was to become a growing controversy concerning the etiology of occupational bladder cancer. He stated that aniline, benzidine, and naphthylamine were the principal etiologic candidates but emphasized that Hamilton [2] had recognized major epidemiologic "pitfalls" including:

a) Worker exposure to more than one suspect compound; further complicated by shifting of workers between departments

b) Different degrees of exposure hazard between processes

c) Unsuspected impurities in trace amounts possibly more harmful than the parent compound

d) Composition of dyes and production methodology in different factories complicating statistical comparison

Despite these "pitfalls" the carcinogenicity of beta-naphthylamine (2-NA) has been well established. As stated by Scott [3] in 1962:

> There is undoubtedly overwhelming evidence that beta-naphthylamine is a highly active carcinogen not only to laboratory animals, but also to man in industrial conditions of manufacture and use, so much so that its manufacture has been given up in Britain and some other countries soley because of the danger associated with it.

Scott [3] considered the manufacture of 2-NA "...to be by far the most hazardous occupation in the dyestuffs industry."

Case [4] in 1952 considered the risk of bladder cancer in workers exposed to 2-NA to be 61 times greater than that in the general population.

The American Conference of Governmental Industrial Hygienists (ACGIH) stated in their Documentation of the Threshold Limit Values [5] that:

> Authorities who have studied the problem appear to be in general agreement that banning the use of this material is justifiable in view of the disastrous consequences to workers who have been engaged in its manufacture and use.

In the past, 2-NA has been used in the dyestuffs industry as an intermediate and in the rubber industry as an antioxidant. Its current commercial usage is considered minimal and its manufacture by the only known source in the United States supposedly ceased in 1972.

Hueper et al [6] provided the first experimental evidence of a carcinogenic potential for 2-NA in 1938 when they induced bladder

cancer in 9 of 16 in dogs injected (s.c.) with various amounts of 2-NA and fed 2-NA in their diet.

Bonser et al [7] administered oral doses of 200 mg, and later 600 mg, of 2-NA in a capsule to 4 female dogs 6 times weekly for a maximum dose of 310 g. Two (2) of the 4 dogs developed bladder tumors in 2 years and in 2 years and 10 months, respectively, following the initiation of treatment. One tumor was malignant and was discovered to be invading the bladder wall when necropsy was performed on this animal a year later.

Boyland et al [8] produced multiple bladder tumors in all 8 female beagles dosed orally with 200 mg, and later 400 mg, of 2-NA contained in capsules and administered 5 times a week. Although multiple tumors were recorded no metastases were observed and it was stated that this was consistent with the experience of others in that distant metastases had never been noted with 2-NA induced tumors.

Deichmann et al [9] investigated the synergism involved with simultaneous oral administration of 2-NA and 4-nitrobiphenyl (4-NBP) to female beagle dogs and discovered this combination to be additive as regards bladder carcinogenic potential. 2-NA, alone, produced malignant bladder tumors in 3 of 4 dogs dosed orally 3 times weekly with a capsule containing 0.1 g of 2-NA.

In 1969, Harrison et al [10] reported the induction of distant metastases in dogs in which bladder tumors had previously been induced following a regime of oral administration of 400 mg of 2-NA a day for 2 years. These metastases were discovered 23 to 55 months later and included lung metastases in 2 of 3 effective animals and renal

metastases in one animal. The results of this study contradicted the earlier hypothesis that bladder tumors induced by 2-NA do not metastasize.

Boyland et al [11] fed Wistar rats a diet containing 0.067 percent 2-NA. Of 12 animals surviving over 700 days the following tumors were observed: bladder papilloma (1), hepatoma (1), bronchogenic carcinoma (1), lung carcinoma (1).

In later papers published in 1961 and 1963 Boyland et al [12,13] injected (i.p.) an inbred strain of rats with 50 mg 2-NA/kg body weight twice weekly until formation of tumors or death. Three of 14 effective animals examined developed tumors; 2 developed abdominal sarcomas and one developed a salivary gland tumor.

Bonser et al [14] produced hepatomas (7/90), subcutaneous scarcomas (12/90), lymphomas (11/90), and benign (1/15) and malignant (1/15) tumors of the intestine in mice injected (s.c.) at weekly intervals with 6 mg of 2-NA to a total dose of 312 mg in 52 weeks.

In a later paper published in 1956 Bonser et al [15] demonstrated that highly purified 2-NA was capable of inducing tumors in mice. Mice received subcutaneous injections of 0.1 ml of a 3 percent solution of 2-NA in arachis oil twice weekly for 50 weeks. The incidence of hepatomas ranged from 8 to 25 percent, respectively, depending upon whether the arachis oil solution of 2-NA was freshly prepared or was permitted to stand prior to injection. Injection site sarcomas were induced in 63 percent of the animals receiving the "older" solution, but in only 17 percent of those receiving the

freshly prepared solution. In each case, however, the 2-NA itself was, as aforementioned, highly purified.

Roe et al [16] tested the possibility of using newborn BALB/c mice in carcinogenicity testing. Of 71 newborn mice injected (s.c.) with 0.02 ml of 1 percent solution of 2-NA (50 μg) in gelatin, 15 (21 percent) developed lung tumors (pulmonary adenomas or adenocarcinomas) and one animal developed a hepatoma. Two of 21 (9.5 percent) vehicle control animals developed lung tumors. The investigators considered these results "doubtful but probably positive." In a later paper published in 1967 these investigators [17] demonstrated that the incidence of pulmonary adenomas in newborn BALB/c mice injected with 2-NA according to the earlier regime [16] was not significantly higher than that in the control group.

Radomski et al [18] injected (s.c.) newborn Swiss mice with a single dose of 30 μg of 2-NA (0.03 ml of a 3 percent suspension of 2-NA in gelatin). Of 63 effective animals autopsied, 6 were discovered with bronchogenic adenomas. No vehicle control animals developed tumors. In a subsequent experiment, newborn Swiss mice were injected on the 1st, 3rd and 5th days of life with 0.03 ml of a 3 percent gelatin suspension of 2-NA (100 μg/dose). The incidence of tumors in these animals did not differ, significantly, from vehicle controls.

Bladder tumors were induced in rhesus monkeys by Conzelman et al [19] as reported in 1969. Monkeys were administered encapsulated doses of 2-NA orally via a stomach tube 6 times weekly. Dosage protocol ranged from 6.25 mg/kg body weight to 400 mg/kg body weight. This protocol was followed for 60 months. Transitional cell

carcinomas of the urinary bladder were induced in 9 of 24 animals within the 60 month exposure period. The earliest carcinoma appeared within 33 months, and one monkey which had received only 12.5 mg/kg for 60 months (total dose of 84 g) developed bladder carcinoma. This finding is contrasted to that in other animals which received higher dosages, up to the maximum of 400 mg/kg, and failed to develop bladder tumors.

The only other species known in which 2-NA has induced cancer of the bladder is the hamster. Saffiotti et al [20-22] induced transitional cell carcinomas of the bladder in this species following a regime of including 2-NA in the diet at a level of 1 percent. Previous attempts at bladder tumor induction with a 0.1 percent 2-NA diet supplement failed to elicit tumor formation in this species. At the higher feeding level 18 of 39 effective animals developed bladder tumors, almost all of which were transitional cell carcinomas. In addition two of the animals developed hepatomas.

An unsuccessful attempt was made by Hueper et al [23] at tumor induction in rabbits injected intraperitioneally or intravenously daily with 3 mg of 2-NA for 9 months. Five of 10 female rabbits in this study, however, developed a pseudo-pregnancy reaction with mammary gland hyperplasia. Some thickening of the urinary bladder was observed, also, in 5 of these animals.

Bonser [24] observed one urinary bladder papilloma in 19 rabbits dosed orally via diet supplement "to the limit of tolerance" for up to 6 years. A similar negative observation was made by Wood [25] in 1970

when no tumors were found in rabbits dosed orally with 100 mg of 2-NA/1.0 ml corn oil 3 times weekly for 65 to 88 weeks.

It is generally considered that 2-NA elicits its tumorigenic effect on the urinary bladder via metabolites. For this reason, much research has been directed toward the identification of those 2-NA metabolites which possess tumorigenic capacity. In general, the observations have been made that ortho- and N-hydroxylated metabolites possess the greater tumorigenic potential of active metabolites thus far identified. Miller and Miller [26] first demonstrated, using 2-acetylaminofluorene, that N-hydroxylation was a step in the production of proximal bladder carcinogens. Clayson [27] postulated that the mandatory ortho-hydroxylation hypothesis which, in its simplest terms states that aromatic amines must undergo ortho-hydroxylation to become carcinogenic, explained the difference in tumorigenic potential between alpha-naphthylamine (1-NA) and 2-NA since the para-position of 2-NA, but not of 1-NA, is blocked, thus effectively preventing formation of para-hydroxylation metabolites of 2-NA, but not of 1-NA.

Manson and Young [25] demonstrated the excretion of 2-NA, 2-acetamido-6-hydroxynaphthalene, and 2-amino-1-naphthylsulfuric acid in rats dosed with 2-NA. These investigators raised the question as to whether 2-amino-6-hydroxynaphthalene and 2-amino-1-hydroxynaphthalene are formed as intermediates during the metabolism of 2-NA.

Benser et al [29] published the results of their study of the comparative metabolism of 2-NA in the dog, mouse, rat, rabbit in 1951 and demonstrated that while the dog excretes 55 to 70 percent of an administered dose of 2-NA as 2-amino-1-naphthol conjugates, the other

species excrete smaller amounts of this form. In a later paper published in 1952, these investigators [30] surgically implanted a paraffin wax pellet impregnated with 1 to 2 mg of either 2-NA or 2-amino-1-naphthol hydrochloride in the urinary bladder of mice. Neither the wax pellet per se nor pellets impregnated with 2-NA induced tumors. Mice into which 2-amino-1-naphthol hydrochloride impregnated pellets were introduced, however, developed papillomas and carcinomas of the bladder.

In 1958 Boyland and Manson [31] published a contemporary listing of the metabolites of 2-NA thus far identified:

1. 2-Acetamidonaphthalene
2. 2-Naphthylsulfamic acid
3. 2-Naphthylamine N-glucosiduronic acid
4. 2-Amino-1-naphthyl hydrogen sulfate
5. 2-Amino-1-naphthyl glucosiduronic acid
6. 2-Amino-1-naphthyl hydrogen sulfate N-glucosiduronic acid
7. 2-Amino-6-naphthol
8. 2-Amino-6-naphthyl hudrogen sulfate
9. 2-Amino-6-naphthyl glucosiduronic acid
10. 2-Acetamido-6-naphthol
11. 2-Acetamido-6-naphthyl hydrogen sulfate
12. 2-Acetamido-6-naphthyl glucosiduronic acid
13. 2-Acetamido-6-hydroxy-5-naphthyl

hydrogen sulfate

14. 2-Acetamido-5,6-dihydro-5,6-dihydroxynaphthalene

15. 2-Acetamido-5:6-dihydro-5:6-dihydroxynaphthalene glucosiduronic acid

Goldblatt et al, [32] utilizing radiolabeled 2-NA, demonstrated that excretion of an intraperitoneally administered dose of 2-NA takes a similar course in the dog, guinea pig, mouse, rabbit and rat, although differences, particularly in fecal excretion, were observed: dog - 3 percent; guinea pig, mouse and rabbit - 10 to 15 percent; rat - 30 percent. Attention was drawn to the fact that small amounts of the administered dose were detectable in the blood for several weeks in the animals used in this study, including the dog. Although at variance with the general concensus, these investigators stated, "We suggest that it is possible that the carcinogenic action in man and dog might be due to small amounts of unchanged amine [2-NA] excreted in the urine . . ." These investigators also demonstrated that radiolabeled 2-NA was rapidly absorbed through the skin of the rat and dog.

In 1959 Troll et al [33] detected di-(2-amino-1-naphthyl) hydrogen phosphate [bis(2-amino-1-naphthyl) hydrogen phosphate] in the urine of dogs dosed with 2-NA. This finding was later confirmed by Boyland et al [34] in 1961. Both Troll et al [33] and Boyland et al [34] considered that this metabolite was a strong candidate as a proximal carcinogen because it was demonstrated in the urine of both dogs and man [35] but not in the urine of rabbits and because its solubility in ether would indicate its facility for cellular

penetration via the lipid membrane and possible intracellular hydrolysis to the ultimate carcinogen.

The N-hydroxylated metabolite of 2-NA, N-hydroxy-2-naphthylamine (N-OH-2-NA), has been demonstrated to be tumorigenic in rats [13] and mice [16,36] and to be present in the urine of both the dog and man. [37-39]

In papers published in 1961 [12] and 1963, [13] Boyland et al compared the carcinogenicity of 2-NA with its N-hydroxylated metabolite, N-OH-2-NA. The results of this experiment indicated N-OH-2-NA to be more carcinogenic than the parent compound when injected intraperitoneally into rats. Ten of 16 rats injected with N-OH-2-NA (50 mg/kg body weight in arachis oil, twice weekly for 3 months) developed tumors (6 sarcomas, 3 carcinosarcomas, 1 lymphosarcoma) while rats similarly injected with 2-NA developed 2 sarcomas and 1 salivary gland tumor. In a later communication, [40] these investigators failed to induce tumors in guinea pigs injected (i.p.) with 24 doses of 20 mg of N-OH-2-NA/kg body weight. They speculated that a species difference in the metabolism of N-OH-2-NA accounted for this resistance as contrasted with the rat.

Walter et al [17] verified the results of Boyland et al [12,13] mentioned above when N-OH-2-NA was demonstrated to induce approximately twice as many lung tumors in neonatal mice as compared with 2-NA when these compounds were given in 5 subcutaneous injections of 100 µg, respectively.

Bonser et al [36] using N-OH-2-NA impregnated in a paraffin wax pellet (12.5 percent suspension) induced 13 bladder tumors in 62 mice (21 percent) compared to 1.2 percent in the vehicle controls.

The ortho-hydroxylated metabolite of 2-NA, 2-amino-1-napthol (1-OH-2-NA), has also demonstrated a carcinogenic potential. Bonser et al [30] implanted paraffin wax pellets containing 1 to 2 mg of either 2-NA or 1-OH-2-NA hydrochloride in the urinary bladder of mice and observed epithelial metaplasia in 1/8 animals given 2-NA and 5 bladder carcinomas, 1 papilloma, and 1 metaplasia in 12 animals given 1-OH-2-NA hydrochloride and surviving 20 weeks or longer.

A later confirmatory investigation published by Bonser et al [36] in 1963 reported the induction of bladder carcinomas in 16.7 percent of a group of 30 mice administered a paraffin wax pellet impregnated with a 12.5 percent suspension of 1-OH-2-NA hydrochloride. The vehicle control animals demonstrated only a 1.2 percent incidence of bladder carcinoma.

The induction of bladder tumors ir workers exposed to 2-NA is one of the most well established cause and effect relationships in occupational medicine. As mentioned earlier, Rehn is credited by Hueper [1] as reporting the first cases of occupational bladder tumors in 1895 in 3 workers in a German dye factory. Much of the early epidemiologic studies were of limited usefulness as concerns specific etiologic roles as Hueper stated in 1934 [1]:

> While aniline, benzidin [sic], and naphthylamine are the substances at the present time mainly accused of responsibility for the production of bladder tumors (International Labor

Office), the exact chemical nature of the causative agent is not known.

Thus for some time the term "aniline cancer" was used to describe occupational bladder cancer in dyestuff workers. In 1938 the total number of known occupational bladder tumors in the world was put at approximately 550 by Hueper. [41] Numerous epidemiologic investigations have proceeded from these earlier reports including limited surveys in the United States. [42-47] However, the industry-wide epidemiologic survey by Case [48] in 1954 is the only in-depth, comprehensive epidemiologic survey undertaken of workers exposed to 2-NA. Case's survey included 4,622 men who had been employed for 6 months or more in the dyestuffs industry. Case estimated that the expected number of death certificates mentioning tumor of the bladder for this population should be 3 to 5 but actually found that of the 262 known cases of bladder tumors in this population, 127 of 144 death certificates mentioned tumor of the bladder. The overall risk of death due to bladder tumor was estimated at 30 times the general population. Of 55 workers, of the 262 total with bladder tumors, who had received exposure to 2-NA only (excluding any exposure to benzidine or 1-NA), 26 of 27 death certificates mentioned the presence of bladder tumors. It was verified that risk of bladder tumors was present in both the manufacture and use of 2-NA. Case estimated the latency period from initiation of exposure to 2-NA to development of tumors to be 16 ± 6 years. In this regard it was also determined that the induction period was constant with respect to age of entry and age

of onset although tumors were observed in workers exposed for less than 5 years or for more than 45 years. Based on the observation that the risk of bladder tumor development increased to a maximum and then decreased, Case suggested that for a given level of risk there are both hypersusceptibles and hyposusceptibles present in the worker population and that selection might be possible by altering the level of risk. However, he considered reduction in employment time to be impractical in eliminating this risk since tumors had been observed in workers exposed for less than 1 year. Case considered that 2-NA was a more potent cause of bladder tumor than benzidine by a factor of 3 and 1-NA by a factor of 5.

Barsotti and Vigliani [49] had earlier observed in an epidemiologic study published in 1952 that 2-NA and benzidine carried the highest carcinogenic potential in the dystuffs industry.

Kleinfeld et al published the results in 1965 [50] and 1967 [51] of an epidemiologic study of workers exposed to 2-NA and other aromatic amines in a dyestuffs plant. Of 376 employees examined, 109 (29.0 percent) were discovered to have bladder malignancies. Of 54 workers exposed only to 2-NA, 17 (31.5 percent) were discovered to have bladder malignancies. The mean latency period for workers exposed only to 2-NA was 20 years with a range of 6 to 38 years. Mixed exposure to 2-NA and benzidine resulted in an incidence of bladder malignancies of 50 percent.

The carcinogenicity of 2-NA is well established by both animal data and human experience. Although an ultimate carcinogenic

metabolite has yet to be identified, this aromatic amine is clearly implicated as a highly hazardous substance in any occupational environment.

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