HAZARD REVIEW

OF

4-NITROBIPHENYL (4-NBP)

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The industrial importance of 4-nitrobiphenyl (4-NBP) was intimately associated with the production of its reduced derivative, 4-aminodiphenyl (4-ADP). With the discontinuance of production of 4-ADP in 1955, principally due to the demonstration by Walpole et al [1] in 1954 that 4-ADP produced carcinoma of the urinary bladder of dogs, the production of 4-NBP was also discontinued. [2]

Because of the structural similarity of 4-ADP and 4-NBP and the possibility of in vivo formation of 4-ADP from 4-NBP, [2] the epidemiologic studies published by Melick et al [3,4] in 1955 and 1971 and by Koss et al [5] in 1969 are of special significance.

In 1955 Melick et al [3] presented the results of their epidemiologic investigation of the incidence of bladder cancer in workers engaged in the production of 4-ADP. Production of this aromatic amine was from 1935 to 1955 in the U.S. Of 171 workers examined in several plants, 11.7 percent developed bladder tumors in 5 to 19 years following initiation of exposure. Exposure duration ranged from 1 to 19 years. In a later report [14] this range increased from 133 days to 35 years. The incidence of bladder tumors increased with time in the study group. In plant 1 the number of workers exhibiting tumors of those examined was 12/71 in 1953 (16.9%), 23/186 in 1958 (12.4%), and 42/261 in 1970 (16.1%). In plant 2 these statistics were 1/44 in 1953 (2.3%), 2/45 in 1958 (4.4%), 10/54 in 1970 (18.5%). The 315 workers examined in this later report by Melick et al [14] were included in a

study by Koss et al [5] published in 1969 of 503 workers examined who had been exposed to 4-ADP. Of the 503 workers examined 435 had no cytologic evidence of bladder cancer, 16 had "suspicious cytology" for carcinoma, 8 had conclusive cytologic diagnosis of carcinoma, 9 had doubtful cytology, and 35 had histologically confirmed carcinoma of the bladder. Of the 24 workers with either suspicious or conclusive cytologic diagnosis of carcinoma, 7 died of unrelated disease prior to histologic proof of bladder carcinoma, 10 were lost to follow-up, and the remaining 7 had no histologic proof of carcinoma. Hence, at the time of the report, it is conceivable that the 35 workers with histologically confirmed carcinoma of the bladder could be expanded to 52, if those workers with positive cytologic examinations were to be found histologically positive. As stated by the investigators, ". . . as evidence from the data previously presented, many years may be required until the clinical proof of cancer is available."

In reviewing the historical implication of 4-ADP as the etiologic agent in the above study by Melick et al, [3,4] Deichmann [6] stated:

> "In reviewing the sequence of historical events, it becomes apparent that Melick et al, had a choice in implicating either 4-nitrobiphenyl or 4-aminobiphenyl, or even both compounds. It is assumed that they decided on 4-aminobiphenyl because of the paper by Walpole et al, [1] and because of our report to the company. Today, I believe we must recognize

that the men in the plant undoubtedly suffered exposure to both 4-aminobiphenyl and 4-nitrobiphenyl. Since both compounds are carcinogenic, both were probably responsible for the tumors reported."

The carcinogenicity of 4-NBP was announced in 1958 by Dieichman at the 7th International Cancer Congress, London, July 1958. [2] This announcement was based on the studies by Diechmann et al [2] initiated in 1955 using 4 mongrel dogs as test subjects. The animals were administered (p.o.) 0.3 g of encapsulated 4-NBP 3 times weekly for the duration of the study and cystoscopic examinations were performed at 5 to 6 month intervals. Malignant bladder tumors were observed in 3 of the 4 dogs at 25, 33, and 33 months, respectively, following the initiation of treatment. The animals had consumed 98 g (7 g/kg) of 4-NBP in 25 months and 130 g (10 g/kg) in 33 months. One animal was negative with regard to bladder tumors at 33 months and dosage was continued.

Comparing total dosage and latency period for dogs administered 4-ADP and 4-NBP, Deichmann et al [2] concluded that 4-NBP was approximately as potent a carcinogen as 4-ADP. As mentioned earlier, these investigators considered the possibility that 4-NBP was reduced *in vivo* and thus exerted its carcinogenic effects as 4-ADP. However, they stated if this was correct, then ". . . it seems surprising that PNB [4-NBP] should be as carcinogenic as PAB [4-ADP], for it is unlikely that the reduction is a quantitive one."

In two later experiments with dogs given lower doses of 4-NBP, Deichmann et al [7 and 8] were unable to duplicate the bladder tumors induced in the earlier experiment [2]. In one of these later experiments published in 1964 [7] dogs were dosed orally with 0.1 g of encapsulated 4-NBP 3 times weekly for 26-31 months and no neoplastic changes were observed in the urinary bladder. However, an additive action was observed when 4-NBP was administered in combination with 2-naphthylamine (2-NA) following the same protocol. It was also considered that 2-NA was more carcinogenic than 4-NBP.

Somewhat similar results were obtained when dogs were dosed as above with 1.0 mg 4-NBP/kg body weight 5 times weekly. After approximately 3 years the animals were sacrificed and the urinary bladders examined for evidence of tumors. No neoplastic changes were observed in any of the animals, although other dogs similarily dosed with 4-ADP developed bladder carcinomas and it was considered that the reason 4-ADP was more carcinogenic than 4-NBP was that the nitro group must first be reduced prior to expression of carcinogenic activity. No evidence of an additive effect, as observed earlier, [7] was observed in this study.

In a paper published in 1969, Deichmann and Radomski [9] concluded that the relative carcinogenic potency of 4-ADP, 2-NA, 4-NBP, and benzidine was 1, 6, 17, and 27, respectively.

Experimental evidence for the <u>in vivo</u> reduction of 4-NBP to 4-ADP was presented in 1960 by Laham [10]. This investigator dosed rats

orally with 16 mg of 4-NBP dissolved in 1 ml of corn oil and examined the urine over a five day interval for metabolites. Evidence was obtained for 4-ADP and 4-amino-3-biphenyl hydrogen sulfate as metabolities of 4-NBP, supporting the hypothesis that 4-NBP must first be reduced to 4-ADP before exerting its carcinogenic effect.

The case for the carcinogenicity of 4-NBP is strongly supported by the induction of bladder carcinoma in dogs, the evidence that 4-NBP is metabolised, *in vivo*, to 4-ADP (a highly carcinogenic aromatic amine), and the possibility that the human cases of bladder cancer attributed by Melick et al to 4-ADP only may have been induced by exposure to 4-NBP as well.

Bibliography for 4-Nitrobiphenyl (4-NBP)

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