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A Comment from the Editor-in-Chief:

The Journal of Occupational Health is the official journal of the Japan Society for Occupational Health. This journal has grown rapidly and now is counted as one of the core journals in occupational health. With enhanced recognition world wide, articles published in our journal now attract much attention. The editorial board therefore decided to create a new section for "Correspondence" from this issue (Vol. 46, No.3) to facilitate communication between authors and readers, believing it will further improve the quality of our journal.

The first correspondence was sent from Bogdanffy et al. concerning the article—Umeda et al (2004 volume 46 number 2 pages 87–99). Umeda et at al showed data indicating that vinyl acetate (VA) at 10,000 ppm by the oral route increases the incidence of neoplasms in mice and rats and concluded that they could "provide clear evidence of VA-induced animal carcinogenicity" for evaluation of 2B made by IARC and JSOH.

Editor-in-Chief
Akio KOIZUMI

Correspondence

Response to Umeda *et al.*

Dear Editor:

On behalf of the Vinyl Acetate Council (www.vinylacetate.org), we wish to provide additional perspective on Umeda *et al*. Carcinogenicity and Chronic Toxicity in Mice and Rats Administered Vinyl Acetate Monomer in Drinking Water, *J Occup Health* 46, 87-99 (2004).

The authors contend the study supports an evaluation of vinyl acetate monomer (VA) as a possible human carcinogen in contrast with previous studies (*e.g.*, Bogdanffy *et al.*[1]), that failed to find treatment related increases in tumor incidence. Based on our review, the results from the present study are of questionable significance to human health as they only substantiate a carcinogenic response at the highest dose (10,000 ppm)—a dose that may have exceeded the maximum tolerated dose (MTD). No other tested dose showed significantly increased tumor incidence in rats or mice of either sex.

The lack of controls for VA hydrolysis by Umeda *et al*. could explain differences from the Bogdanffy *et al*. findings. Bogdanffy *et al*. described hydrolytic or evaporative losses necessitating daily preparation of drinking water solutions. Umeda *et al*. prepared drinking water solutions twice weekly, thereby exposing animals to a very acidic (pH 3.6) mixture containing VA and about 3% acetic acid and acetaldehyde at 10,000 ppm. Since acetic acid is known to be a tumor promoter (Slaga *et al*.[2]), the responses reported by Umeda *et al*. may relate to hydrolysis products and pH of the dosing solution.

It is likely that the MTD was exceeded at 10,000 ppm based on the large reductions in body weight and water intake, and disruptions in tissue homeostasis. Valentine *et al*.[3] reported a 2-fold increase in oral cavity cell proliferation in mice following 3 months of exposure to 10,000 ppm VA, yet no significant changes occurred at 5,000 or 1,000 ppm. The observation that neoplastic and preneoplastic changes occurred in mice only where cell proliferation was significantly elevated, suggests that the MTD for tissue homeostasis was exceeded at 10,000 ppm.

Without supportive information, Umeda *et al*. derived a Benchmark Dose (BMD) with VA intake (mg/kg/day) as the dose metric. Their BMD analysis employed an unorthodox approach that combined male and female rat and mouse data; in contrast, common practice is to separately analyze data for each species/sex.

Absent additional mechanistic data, this BMD "meta-analysis" can only be considered speculative. Other factors such as the VA flux rate into target tissues, possible sex/species differences in oral cavity surface area, and rates of key metabolic enzymes must be accounted for quantitatively to properly normalize VA dose across species and sex. These considerations argue strongly for separate BMD analyses by species/sex and subsequent normalization based on VA absorbed and metabolized in the oral cavity.

Since oral cavity tumor incidence was significantly increased only at 10,000 ppm, the BMD approach cannot provide useful information about the shape of the true dose-response curve. A threshold may exist, with the breakpoint between 5,000 and 10,000 ppm. Recall Bogdanffy *et al*. saw no increase in oral cavity tumors among rats exposed to 5,000 ppm VA.

In summary, the findings of Umeda *et al*. may bear little relevance to potential human health risks from low-level exposure. Extensive mechanistic research has shown that the mode of carcinogenic action of VA is a threshold process involving at least five steps for cancer development (Bogdanffy and Valentine[4]). VA-induced cell proliferation from metabolically formed acetic acid and acetaldehyde is a critical prerequisite. The fact that only the 10,000 ppm level produced a significant incidence of non-neoplastic and neoplastic lesions is consistent with this threshold mechanism. An alternative to Umeda *et al*.'s conclusion from these data is that extremely high lifetime exposure is required for VA to induce proliferative and neoplastic responses.

Matthew Bogdanffy
DuPont Haskell Laboratory
Rudolph Valentine
DuPont Haskell Laboratory
Dawn Goodman
Covance Laboratories Inc.
Consultant to Vinyl Acetate Council
Thomas Starr
TBS Associates
Consultant to Vinyl Acetate Council

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2) TJ Slaga, GT Bowden and RK Boutwell: Acetic acid, a potent stimulator of mouse epidermal macromolecular synthesis and hyperplasia but with weak tumor-promoting ability. JNCI 55, 983–987 (1975)
3) R Valentine, JR Bamberger, B Szotek, SR Frame, JF Hansen and MS Bogdanffy: Time- and concentration-dependent increases in cell proliferation in rats and mice administered vinyl acetate in drinking water. Toxicol Sci 67, 190–197 (2002)
4) MS Bogdanffy and R Valentine: Differentiating between local cytotoxicity, mitogenesis, and genotoxicity in carcinogen risk assessments: the case of vinyl acetate. Toxicol Lett 140/141, 83–98 (2003)

Correspondence to: Vinyl Acetate Council, 1250 Conneticut Avenue, N.W. Suite 700, Washington, D.C. 20036, USA (e-mail: info@vinylacetae.org)

Correspondence

Response to Dr. Bogdanffy *et al.*'s comments on our paper

We would like to respond to Dr. Bogdanffy *et al.*'s comments.

Although Bogdanffy *et al.* insisted that we used "a mixture containing VA and about 3% acetic acid and acetaldehyde at 10,000 ppm", we detected 0.0263% (w/w) of acetic acid (AA) in the 10,000 ppm vinyl acetate (VA)-formulated drinking water after the 4-day administration period. The level of 0.0263% was far below the AA levels of 33 to 667 μmoles (equivalent to 1 to 20%) which were reported to exhibit very weak tumor promoting ability[1]. We consider that there is tumor response to VA but not AA.

We do not agree with their comment that the highest dose level of 10,000 ppm VA used in our study exceeded the Maximum Tolerated Dose (MTD). The body weight of the rats given 10,000 ppm decreased by less than 10%, and their survival rates did not decline when compared to the controls. A greater than 10% decrease in body weight gain of the mice given 10,000 ppm was observed near the end of the 104-wk period, but their survival rates did not decline when compared to the controls. The greater than 10% decrease in the body weight of mice given 10,000 ppm can be observed after the 78th wk for males and the 84th wk for females, both of which were coincident with the time that oral cavity tumor death started to occur (Fig. 1). We can conclude on the basis of the MTD criteria of the OECD Guidelines[2] that the highest dose level does not exceed the MTD in our cancer bioassay study.

Bogdanffy *et al.* suggested that the MTD for tissue homeostasis was exceeded at 10,000 ppm. Valentine, Bogdanffy and their associates[3] reported that oral cell proliferation significantly increased in mice after 3 months of exposure to 10,000 ppm VA, whereas no significant changes occurred at 5,000 and 1,000 ppm. We think that neoplastic and pre-neoplastic proliferative lesions, indicative of altered tissue homeostasis, occur at

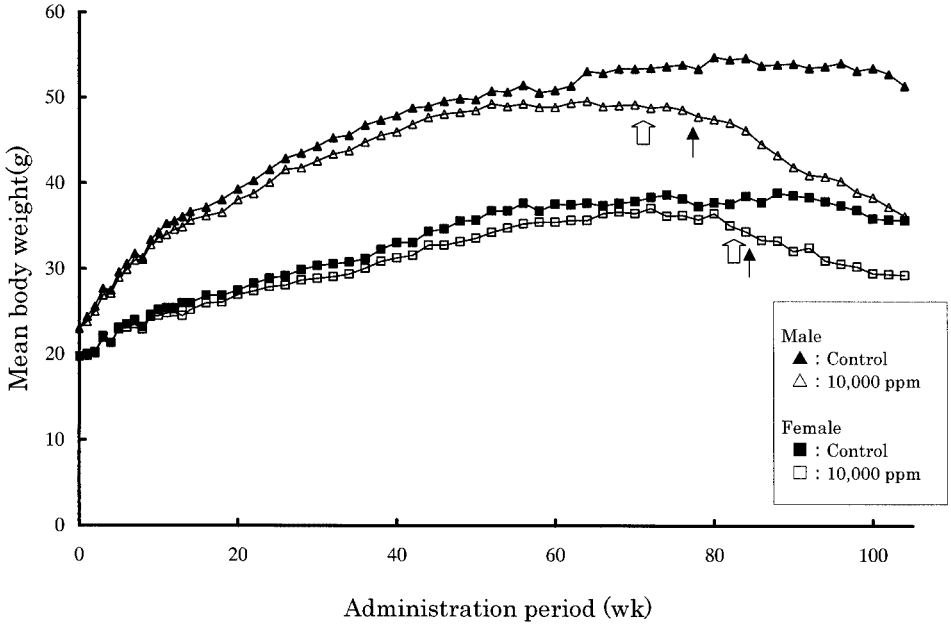

Fig. 1. Time-course change in body weight of male and female mice given 0 and 10,000 ppm VA in drinking water.

↑ : The first time point at which a decrease of greater than 10% in body weight gain as compared to the control was observed.

⇧ : The first time point at which oral cavity tumor death started to occur.

Correspondence to: Y. Umeda, Japan Bioassay Research Center, Japan Industrial Safety and Health Association, 2445 Hirasawa, Hadano 257-0015, Japan (e-mail: yumeda@jisha.or.jp)

10,000 ppm which does not exceed the MTD.

As to their comments on our BMD approach with daily VA intake and combined incidences of oral cavity squamous cell tumors in mice and rats of both sexes, we attempted to quantitatively delineate a dose-response (tumor incidence) relation for cancer risk assessment with a multistage model as a function of the estimated VA intake (internal dose), instead of the bottle concentration of VA. We thought that the incidence of oral cavity tumors (tumor response) might depend on the daily amount of VA to which the oral cavity squamous cells were exposed through drinking. It is interesting to note that the incidence of oral cavity tumors induced by oral administration of 5,000 ppm VA to mice (Maltoni *et al.*[4]) and two cases of oral cavity squamous cell carcinomas in the male rats given 5,000 ppm VA (Bodganffy *et al.*[5]) follow the internal dose-tumor response curve (Fig. 6 in our paper).

Yumi Umeda
Michiharu Matsumoto
Kazunori Yamazaki
Makoto Ohnishi
Heihachiro Arito
Kasuke Nagano
Seigo Yamamoto
Taijiro Matsushima

Japan Bioassay Research Center, Japan Industrial Safety and Health Association, 2445 Hirasawa, Hadano 257-0015, Japan

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