CHEMICAL MEETING THE CRITERIA FOR LISTING AS CAUSING REPRODUCTIVE TOXICITY VIA THE AUTHORITATIVE BODIES MECHANISM

1,3-BUTADIENE IDENTIFIED BY NIOSH AND U.S. EPA

PACKAGE 5h

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Reproductive and Cancer Hazard Assessment Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

1,3-Butadiene (CAS No. 106-99-0) meets the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism as known to the State to cause reproductive toxicity (developmental, male reproductive and female reproductive endpoints). The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The National Institute for Occupational Safety and Health (NIOSH) and the U.S. Environmental Protection Agency (U.S. EPA) have been identified as authoritative bodies for purposes of Proposition 65 (22 CCR Section 12306(l)) and both organizations have formally identified 1,3-butadiene as a chemical causing developmental and reproductive toxicity.

OEHHA has found that 1,3-butadiene has been "formally identified" by NIOSH (1984) and U.S. EPA (1989, 2002) as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306(d)). The chemical is the subject of reports which are published by the authoritative bodies and which conclude that the chemical causes reproductive toxicity (NIOSH, 1984; U.S. EPA, 1989, 2002) (22 CCR 12306(d)(1)), and the documents specifically and accurately identify the chemical and have been "published by the authoritative body in a publication, such as, but not limited to, the federal register for an authoritative body which is a federal agency" (22 CCR 12306(d)(2)(C)).

OEHHA also finds that the criteria given in regulation for "as causing reproductive toxicity" (22 CCR 12306[g]) have been satisfied for the 1,3-butadiene. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative bodies in making their finding that the specified chemical causes reproductive toxicity. A brief discussion of the relevant reproductive and developmental toxicity studies providing evidence for the findings is presented below. Much of the discussion is taken verbatim from the U.S. EPA (2002) report. The statements in bold reflect data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for reproductive toxicity (22

CCR 12306[g]). The full citations for the authoritative body documents are given in this report.

Manifestations of male and female reproductive toxicity include testicular and ovarian atrophy in mice and dominant lethal effects.

Manifestations of developmental toxicity include reduced fetal growth and increased morphological abnormalities from in utero exposure to 1,3-butadiene.

NIOSH (1984) concluded: "There is a possible reproductive hazard to workers exposed to 1,3-butadiene based on maternal and fetal toxicity observed in 1,3-butadiene exposed rats; an indication of teratogenicity in exposed rats; and suggestion of testicular and ovarian atrophy in mice exposed to 1,3-butadiene." "It is recommended that 1,3-butadiene be regarded as a potential occupational carcinogen, teratogen, and as a possible reproductive hazard." "These recommendations are based on long-term animal studies which demonstrated carcinogenicity, teratogenicity and adverse effects upon the testes and ovaries."

In its 1989 document *Health and Environmental Effects Document for 1,3-Butadiene,* U.S. EPA (1989) concluded that: "Chronic inhalation exposure to 1,3-butadiene…caused gonadal atrophy in both sexes of B6C3F1 mice (NTP, 1984)." "Data from Hazleton Laboratories [(Owen and Irvine, 1981)] indicate that 1,3-butadiene is a teratogen when pregnant female rats are exposed by inhalation at 8000 ppm (17,698 mg/m3) 6 hrs/day during organogenesis."

In its 2002 document *Health Assessment of 1,3-Butadiene,* U.S. EPA (2002) concluded that: "1,3-butadiene also causes a variety of reproductive and developmental effects in mice. … The most sensitive effect was ovarian atrophy observed in a lifetime bioassay of female mice." "The reproductive and developmental effects of 1,3-butadiene are among the health effects (both cancer and non-cancer) observed at the lowest exposure levels following short-term or chronic inhalation exposure."

In support of these conclusions, NIOSH (1984) and U.S. EPA (1989, 2002) cited an inhalation study of pregnant Sprague-Dawley rats exposed at 200, 1,000, or 8,000 ppm of 1,3-butadiene for 6 hours per day on days 6-15 of gestation which produced dose-related maternal and fetal toxicity when compared to an unexposed group of controls (Owen and Irvine, 1981). Depressed body weight gain among dams was observed at all concentrations, and fetal growth was significantly retarded among rats exposed at the 8,000 ppm. Fetal deaths, though not statistically significant, were higher than controls for all exposed groups, and at 8,000 ppm, a statistically significant increase in major skeletal abnormalities was recorded (skull, spine, sternum, long bones and ribs). NIOSH (1984) and U.S. EPA (1989, 2002) also cited a study in mice exposed at 1,3-butadiene concentrations of 625 or 1,250 ppm, 6 hours per day, 5 days per week for 61 weeks (Powers, 1983). 1,3-butadiene was associated with the induction and early onset of atrophy of the ovaries and testes. U.S. EPA (1989) also cites an abstract of a Russian

study (Serebrennikov and Ogleznev, 1978) which reported that inhalation of 1,3-butadiene caused embryo mortality and teratogenesis.

In support of these conclusions, U.S. EPA (2002) also cited a variety of additional reproduction studies: one in rats (Bevan et al., 1996); three in mice (NTP, 1984 [same as Powers, 1983], 1993; Bevan et al., 1996); and an acute "sperm head morphology" study in B6C3F1 mice (Hackett et al., 1988); several dominant lethal/mutagenicity studies in mice (Hackett et al., 1988; Anderson et al., 1993, 1995, 1996, 1998; Adler and Anderson, 1994; Brinkworth et al., 1998; Paccierotti et al., 1998) and rats (Anderson et al., 1998); as well as a developmental toxicity study in rats (IISRP, 1982) and a study in mice (Hackett et al., 1987). These studies are described below. The descriptions of the studies are mostly taken verbatim from U.S. EPA (2002).

Bevan et al. (1996)
Groups of male and female rats and mice were exposed by inhalation to 1,000 ppm 1,3-butadiene for 6 hr/day, 5 days/wk for 13 weeks. Exposed male and female rats and mice showed no effects on body weight or weight gain, but there was an increase in absolute and relative liver weights, and male rats had increased relative kidney weights with hyaline droplet accumulation in renal proximal tubules. There were no clinical chemistry or hematologic effects in rats. There was a significant decrease in circulating erythrocyte mass and an increase in reticulocyte counts in both male and female mice; male mice had mild macrocytic anemia. The most remarkable finding was ovarian atrophy in 6/10 female mice. All treated male mice showed reduced testicular weights and testicular atrophy. U.S. EPA noted that these data demonstrate that ovarian and testicular atrophy can develop as early as 13 weeks after exposure to a high concentration of 1,3-butadiene.

NTP (1984)
National Toxicology Program (NTP, 1984) exposed male and female mice to 0, 625, or 1,250 ppm 1,3-butadiene 6 h/day, 5 days/week. Animals were killed after 60 or 61 weeks of exposure. Among female mice, ovarian atrophy was seen in 40/45 (89%) mice exposed to 625 ppm and in 40/48 (83%) mice exposed to 1,250 ppm, compared with an incidence of only 2/49 (4%) in control mice. Involution of the uterus, which was considered a manifestation of ovarian atrophy, was seen in 7/46 (15%) and 14/49 (29%) mice exposed to 625 and 1,250 ppm, respectively, compared with 0/49 control mice. Uterine involution was characterized by fewer and less prominent endometrial glands. Testicular atrophy was observed in 19/47 (40%) mice exposed to 625 ppm and in 11/48 (23%) mice exposed to 1,250 ppm compared with 0/50 control mice. Statistical analysis showed that the increased incidences of the gonadal lesions in male and female mice were significant ($p<0.05$) for all groups compared with their respective controls.

NTP (1993)
NTP (1993) conducted a second inhalation chronic bioassay study in male and female B6C3F1 mice exposed to lower concentrations of 1,3-butadiene. Concentrations were 0, 6.25, 20, 62.5, 200, or 625 ppm 1,3-butadiene for 6 h/day, 5 days/week for 103 weeks, with interim evaluations at 9 and 15 months. Additional male mice were exposed to 200 ppm of 1,3-butadiene for 40 weeks or 625 ppm for 13 weeks (8,000 ppm. weeks), or 312

ppm for 52 weeks or 625 ppm for 26 weeks (16,000 ppm. weeks), followed by observation for the remainder of the 2 years (stop-exposure protocol). This study was designed to study neoplastic and general toxicological, rather than reproductive, endpoints. Ovarian atrophy was seen in the 200 ppm and 625 ppm exposure groups sacrificed for the 9-month interim evaluation. The atrophic ovaries were characterized by the absence of oocytes, follicles, and corpora lutea. No occurrences of this lesion were noted in the lower exposure groups. Hyperplasia of the germinal epithelium was observed in one animal exposed to 625 ppm for 9 months. Germinal epithelial hyperplasia was described as prominent down-growth of the mesothelial surface into the parenchyma of the ovary, forming tubular and glandlike structures. At the 15-month interim evaluation, ovarian atrophy was observed in mice exposed to 20 ppm or higher, with a significant increase in the incidence at 62.5 ppm or higher compared with concurrent controls. Hyperplasia of the germinal epithelium was seen at 200 and 625 ppm but was not significant. Angiectasis (dilation of blood vessels) was seen in one mouse in the control group, one exposed to 6.25 ppm, and two exposed to 200 ppm. The ovary, which was evaluated at 15 months in only two female mice exposed to 625 ppm, was atrophic in both. Among female mice exposed to 1,3-butadiene for 2 years, ovarian atrophy was observed in all exposure groups at incidences that were significantly elevated compared with controls. Although the functional integrity of the female reproductive system was not assessed, U.S. EPA noted that it can be assumed that animals without oocytes or follicles would be infertile and would express reduced estrogenic and progestin secretory capacities.

Uterine atrophy was seen at the two highest concentrations at 9 months, but was seen only at the highest concentration at the 15-month evaluation. After 2 years, the incidence of uterine atrophy among mice exposed to 200 and 625 ppm did not increase relative to that observed at 9 months.

The testes of a majority of male B6C3F1 mice exposed to the highest concentration of 1,3-butadiene (625 ppm) were atrophic at the 9- and 15-month interim evaluations and at termination of the 2-year study. In the stop-exposure study, testicular atrophy was observed after 2 years in 5/50 mice exposed to 200 ppm 1,3-butadiene for 40 weeks and 3/50 exposed to 625 ppm for 13 weeks (8,000 ppm. weeks), and in 3/50 mice exposed to 312 ppm for 52 weeks and 5/50 exposed to 625 ppm for 26 weeks (16,000 ppm. weeks). U.S. EPA noted that the lack of a more prominent response in mice exposed to 625 ppm for 26 weeks may have been due to insufficient time for induction of testicular atrophy or, if atrophy was induced during exposure, the possibility of lesion repair following termination of the exposure and before the examination at 2 years.

Hackett et al. (1988)

This sperm-head morphology study was conducted in B6C3F$_1$ mice at Pacific Northwest Laboratories for NTP as part of a series of studies to investigate the effects of 1,3-butadiene on reproductive function. Adult male B6C3F$_1$ mice were exposed to 1,3-butadiene at target concentrations of 0 (filtered air), 200, 1,000, or 5,000 ppm 6 h/day for 5 successive days. Mice were killed 5 weeks after exposure, weighed, and examined for gross lesions, with particular emphasis on the reproductive tract. Sperm collected from

the right epididymis were examined for abnormal heads (blunt hook, banana, amorphous, pinhead, two heads/two tails, short) and other abnormalities (primarily midpiece abnormalities).

Piloerection and dyspnea were observed within the first 20 to 30 min after exposure in mice receiving 5,000 ppm; no clinical signs of toxicity were noted for the other groups. The percentages of epididymal sperm with normal morphology were 98.08%, 97.23% ($p<0.05$), and 96.34% ($p<0.05$) at 200, 1,000, and 5,000 ppm, respectively, compared with 98.40% for controls; these values also showed a significant exposure-related trend ($p<0.05$). The percentages of the following abnormalities were significantly elevated compared with controls ($p<0.05$): blunt hooks at 5,000 ppm, bananas at 1,000 and 5,000 ppm, and pinheads at 1,000 ppm. Amorphous, two heads/two tails, and shorts were not significantly elevated at any dose. The predominant types of abnormalities were the banana followed by blunt hook and amorphous. The authors speculated that late spermatogonia or early primary spermatocytes were sensitive to 1,3-butadiene. The authors also stated that examining the sperm at only one time point following termination of exposure precluded a determination of the stage of spermatogenesis affected by the chemical.

In the dominant lethal component of the study, CD-1 mice were exposed by whole-body inhalation to 200, 1,000, and 5,000 ppm 1,3- butadiene for 6 h/day on 5 consecutive days. A significant increase in the number of early deaths of implants per pregnant female was observed during the first 2 weeks after exposure, but the results were not dose related. Males exposed to 200 ppm and 1,000 ppm sired litters with increased numbers of early deaths. This effect was not seen in the group exposed to 5,000 ppm. In addition, in the first week post-exposure the number of dams showing two or more dead implants per pregnancy was increased for all dose groups. Because these effects were noted in the first week or two following exposure, the authors suggested that spermatozoa and spermatids were the susceptible germinal stage.

Anderson et al. (1993)
In this dominant lethal study, male CD-1 mice received acute and subchronic inhalation exposures to 1,3-butadiene and were then mated to untreated females. In the acute study, the male mice were exposed to 0, 1,250, or 6,250 ppm for 6 h. The females were examined for live fetuses, postimplantation deaths, and gross malformations. The only statistically significant result was a small decrease in implantations at 1,250 ppm. In the subchronic study, the males were exposed to 0, 12.5, or 1,250 ppm for 6 h/day, 5 days/week for 10 weeks. Statistically significant effects were observed at both exposure levels. An increase in late deaths and abnormal fetuses was observed at 12.5 ppm. A decrease in the number of implantations and an increase in the number of dominant lethal mutations were found at 1,250 ppm, as well as an increase in fetal malformations. Further evaluation of the fetuses as well as evaluation of animals allowed to deliver their young was published in a report and a paper by Anderson et al. (1995, 1996). In fetuses recovered on gestation day 17, skeletal changes were evaluated in the small number of malformed fetuses and their normal litter mates and controls, and karyotypes were

examined from the livers of these fetuses. A few minor skeletal changes were seen in the skeleton, particularly in skull bones of fetuses with exencephaly.

Adler and Anderson (1994)

In this study, male (102/E1 × C3H/E1)F1 mice were used to assess the stage at which male germ cells are affected by 1,3-butadiene. Adult males were exposed by inhalation to 0 or 1,300 ppm, 6 h/day for 5 consecutive days. Four hours after the end of exposure, each male was mated at a ratio of 1:2 to untreated virgin females. Females judged bred by the presence of a vaginal plug were replaced with new females, and mating continued for 4 consecutive weeks. Females were killed on gd 14 to 16 and examined for numbers of live and dead implants. Exposure of male mice to 1,300 ppm resulted in an increase in dead implants during the first to the third weeks of mating; however, statistical significance ($p<0.01$) was reached only in the second week. When expressed as a percentage of dominant lethals, a significant increase was seen in the second (12.4%, $p<0.01$) and third (5.5%, $p<0.05$) weeks. Because of the time course for dominant lethal mutations to manifest as dead implantations, 1,3-butadiene again appears to induce dominant lethality in spermatozoa and late spermatids.

Brinkworth et al. (1998)

CD-1 mice, aged 8-10 weeks were exposed to either 0, 12.5, or 125 ppm 1,3-butadiene. The purpose of this study was to undertake a dominant lethal study in mice at sub-chronic low dose (6 h/day, 5 days/wk, 10 weeks) exposure to 1,3-butadiene. CD-1 mice, aged 8-10 weeks were assigned to 3 groups and exposed to either 0, 12.5, or 125 ppm 1,3-butadiene and then mated to untreated virgin females. Incidence of early deaths were significantly elevated in the 125 ppm dose group relative to the control group ($p<0.01$). The incidence of late deaths and of dead fetuses was higher in both dose groups than in the control, but the difference was not statistically significant.

Anderson et al. (1998)

This study tested the hypothesis that genetic effects could be transmitted by males to their offspring following subchronic inhalation exposure to 1,3-butadiene in mice and rats. Male CD-1 mice were exposed to 0 ppm, 12.5 ppm, 65 ppm, or 130 ppm for 6 h/day, 5 days/wk, for 4 weeks. Male Sprague-Dawley rats were exposed to 0 ppm, 65 ppm, 400 ppm, or 1,250 ppm for 6 h/day, 5 days/wk, for 10 weeks. Each exposed male was mated with two untreated virgin females. Females were killed the day before parturition (day 17 after finding a vaginal plug in mice and on day 19 after finding a sperm-positive vaginal smear in rats). Females were examined for the number of live fetuses, the number of fetuses with gross malformations, and the number of postimplantation early and late deaths. In mice there was a significant increase in the mean number of early embryonic deaths in the 65 and 130 ppm dose groups. In rats, there was a statistically significant ($p<0.05$) reduction in implants in the 65 ppm exposure group, but not in the 400 and 1,250 ppm dose groups.

Pacchierotti et al. (1998)

In this study, a cytogenetic analysis of chromosome aberrations in first-cleavage embryos derived from 1,3-butadiene exposed male mice was conducted. Male (102/E1 × C3H/E1) mice were exposed for 5 consecutive days (6 h/day) to 0, 130, 500, or 1,300 ppm of 1,3-butadiene in air. On the last day of inhalation exposure, mice were mated during a 3-week period with untreated females for evaluation of transmissible chromosome damage. First cleavage fertilized oocytes following paired matings were analyzed for chromosome and chromatid break and exchange aberrations for each dose group. Statistically significant increases over controls were observed in the first mating week of mice exposed to 500 and 1,300 ppm doses and in the second mating week of animals treated at the 1,300 ppm dose. There was no evidence of increased frequency of zygote aberrations obtained from animals in third week matings. Aberration induction was 2.5 times higher in the first than in the second mating week. U.S EPA noted that this suggested that late developmental stages of spermatozoa were again more sensitive to butadiene than earlier stages. Of 72 aberrations observed, 96% of them were chromosomal breaks or exchanges.

IISRP (1982)

Pregnant Sprague-Dawley CD rats were exposed by inhalation to 1,3-butadiene at target concentrations of 0, 200, 1,000, or 8,000 ppm 6 h/day on gestation day (gd) 6 to 15 and killed on gd 20. Maternal body weight gain was markedly depressed in dams exposed to 1,000 and 8,000 ppm, especially during gd 6 to 9; a significant decrease was also noted during gd 9 to 12 in rats exposed to 8,000 ppm. During the later stages (gd 12 to 15 and 16 to 20), body weight gain was similar to controls. The gravid uterus and extragestational weights were similar to controls, but extragestational weight gain was significantly depressed by 17% ($p<0.05$) in dams exposed to 1,000 ppm and by 24% in dams exposed to 8,000 ppm ($p<0.05$). No effects were observed on other measures of maternal toxicity. Fetal body weight and crown/rump length were significantly reduced at 8,000 ppm ($p<0.05$). The percentage of fetuses with major skeletal defects was significantly elevated at 1,000 and 8,000 ppm and minor skeletal defects were significantly elevated only at the lowest concentration. The percentage of fetuses showing minor external/visceral defects, predominantly subcutaneous hematomas, was significantly elevated only at 1,000 ppm, but the percentage was similar in all three experimental groups. The incidence of bilateral lens opacity was elevated at all concentrations but was significantly elevated only at 8,000 ppm. The incidence of marked-to-severe wavy ribs and the total number of abnormal ossifications and irregular ossification of the ribs were elevated at 8,000 ppm. The incidence of thoracic bipartite centers was elevated in all exposed groups; a dose-response relationship was not observed.

Hackett et al. (1987)

Pregnant CD-1 mice were exposed to target concentrations of 0, 40, 200, or 1,000 ppm 1,3-butadiene 6 h/day on gd 6 to 15. Three animals exposed to 1,000 ppm showed signs of dehydration: two died on gd 15, and early parturition occurred in the third. No other clinical signs of toxicity were observed. Exposure-related decreases in whole-body weights on gd 18, body weight gain during gd 11 to 16, gravid uterine weight,

extragestational weight, and extragestational weight gain were significantly reduced in the 1,000 ppm exposure group compared with controls. Whole-body weight gain during gd 11 to 16 and extragestational weight gain were also reduced in the 200 ppm exposure group. None of these parameters were significantly affected in dams exposed to 40 ppm.

More resorptions per litter were observed among control dams than among exposed dams. Fetal body weights were reduced in all exposed groups compared with controls, and the reduction showed a significant exposure-related trend. The overall fetal body weights (males and females combined) were reduced by 4.5% at 40 ppm (not significant), 15.7% at 200 ppm ($p<0.05$), and 22.4% at 1,000 ppm ($p<0.05$). Significant differences from controls were seen at all treatment concentrations for fetal males and at the two higher concentrations for fetal females. Placental weights showed an effect similar to that of fetal body weights. Malformations occurred sporadically and at low frequencies in all exposure groups; increases were seen in several skeletal variations. The frequency of supernumerary ribs was greatly elevated at 200 and 1,000 ppm; 6% of the fetuses/litter were affected at 200 ppm ($p<0.05$) and 9.9% at 1,000 ppm ($p<0.05$) compared with 1.7% in controls and 1.6% in the 40 ppm exposure group (not significant). There also was a marked increase in the total number of fetuses with supernumerary ribs at the 200 and 1,000 ppm exposure levels. A number of these were of normal length as opposed to those considered rudimentary ribs or ossification sites at lumbar 1. The frequency of reduced ossification of the sternebrae was elevated at 200 ($p<0.05$) and 1,000 ppm ($p<0.001$) (Fisher exact test); the litter incidence was elevated but not significantly. The percentages of reduced ossifications at all sites and the percentages of abnormal sternebrae (misaligned, scrambled, or cleft) per litter were also significantly elevated at 1,000 ppm ($p<0.05$). The percentages of supernumerary ribs and abnormal sternebrae also showed significant linear trends.

U.S. EPA concluded that in these studies1,3-butadiene caused developmental effects, manifested by reduced fetal body weight and increased frequency of skeletal variations at 200 and 1,000 ppm. U.S. EPA also concluded that 1,3-butadiene caused a significant reduction in body weight of male fetuses at 40 ppm and, further, the dose-related increases in supernumerary ribs and reduced ossifications in mice, particularly of the sternebrae, indicate altered development and are a cause for concern.

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