RESPONSE TO THE PETITION OF BAYER CORPORATION FOR CLARIFICATION OF THE PROPOSITION 65 LISTING OF "MERCURY AND MERCURY COMPOUNDS" AS CHEMICALS KNOWN TO CAUSE REPRODUCTIVE TOXICITY

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

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I. The Petition

On October 15, 2003, a petition on behalf of Bayer Corporation "for reconsideration of the determination that a 1984 EPA report formally identified 'mercury and mercury compounds' as reproductive toxins and clarification of the listing" ("Petition") was filed with the Office of Environmental Health Hazard Assessment (OEHHA) by Norman C. Hile of Orrick, Herrington & Sutcliffe, LLP. The Petition specifically seeks "to discern whether OEHHA interprets the 'mercury and mercury compounds' listing to encompass thimerosal and PMA [phenylmercuric acetate]." Bayer requests that if OEHHA interprets the "mercury and mercury compounds" listing under Proposition 65 to encompass thimerosal or PMA, the listing should be reconsidered. If OEHHA finds the converse that the listing did not encompass thimerosal and PMA, then Bayer requested a clarification of the listing.

The general assertions of the Petition are summarized below.

1. The U.S. Environmental Protection Agency (U.S. EPA) "does not now – and has not ever – formally identified either thimerosal or PMA as a reproductive toxin" because:
   - i) The 1984 U.S. EPA report[1] does not specifically and accurately identify thimerosal, much less conclude it causes reproductive toxicity.
   - ii) The 1984 U.S. EPA report specifically and accurately identifies PMA but does not conclude that PMA causes reproductive toxicity within the meaning of Title 22, California Code of Regulations section 12306(g).
1. Since neither thimerosal nor PMA have ever been identified as reproductive toxins, the criterion of Title 22, Cal. Code of Regulations, section 12306(j)(2) for reconsideration is met.
2. If OEHHA does not clarify that the listing of "mercury and mercury compounds" does not include thimerosal and PMA, reconsideration of these chemicals by the Developmental and Reproductive Toxicant (DART) Identification Committee is required.
3. If OEHHA clarifies that the listing of "mercury and mercury compounds" does not include thimerosal and PMA, then full reconsideration is not necessary.

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[1] "Mercury Health Effects Update: Health Issue Assessment," EPA-600/8-84-019F, U.S. Environmental Protection Agency, Office of Research and Development, 1984.

4. If OEHHA believes other authoritative bodies identify thimerosal and PMA as a reproductive toxicant, OEHHA must formally propose expansion of the listing to include them, although Bayer's review of the literature did not uncover an authoritative body that formally identifies PMA or thimerosal within the meaning of Title 22, California Code of Regulations section 12306(g).

OEHHA's general response to the Petition follows in section II. Since the issue of the scope and appropriateness of the listing of mercury and mercury compounds has previously been raised and litigated, a brief history of their listing under Proposition 65 is then provided. This is followed by an analysis to determine whether reconsideration of thimerosal and PMA as requested is appropriate, and OEHHA's analysis of specific arguments and issues raised in the Petition. The Appendix describes various documents published by Proposition 65 authoritative bodies that make statements about the reproductive toxicity of mercury and mercury compounds.

II. Summary of Response to Bayer Petition

The Safe Drinking Water and Toxic Enforcement Act of 1986, (Health and Safety Code section 25249.5 et seq.) commonly known as Proposition 65 requires the Governor to maintain a list of chemicals known to the State of California to cause cancer or reproductive toxicity. Reproductive toxicity may include either or both developmental and reproductive harm. Chemicals are added to the Proposition 65 list through several procedures, including the "authoritative bodies" mechanism described in Title 22, Cal. Code of Regulations section 12306. The listing at issue in this petition occurred through the "authoritative body" listing process based upon a 1984 document published by U.S. EPA.

The procedures for reconsideration of chemicals listed as causing reproductive toxicity under Proposition 65 via the authoritative bodies mechanism are provided in Title 22, Cal. Code of Regulations section 12306(j)[2]: When the lead agency finds that 1) there is no substantial evidence that the criteria for "as causing reproductive toxicity" (i.e. Section 12306(g)) have been satisfied, or 2) the chemical is no longer identified as causing reproductive toxicity by the authoritative body, then the agency must reconsider its determination that the chemical has been formally identified as causing reproductive toxicity. If either of the two criteria for reconsideration is satisfied, the chemical is then referred to the DART Identification Committee. In response to Bayer's Petition, these criteria were applied to the evidence and documentation encompassing the listing of thimerosal and PMA.

Thimerosal and PMA have been included on the Proposition 65 list since 1990 when the listing for mercury and mercury compounds was made, because each is a mercury compound. Based upon our review of the documents supporting the listing of mercury and mercury compounds,

[2] All further references are to Title 22 of the California Code of Regulations, unless indicated otherwise.

OEHHA finds that neither of the reconsideration criteria is met for thimerosal or PMA. With regard to the first criterion, the scientific evidence that PMA and thimerosal cause reproductive toxicity is clear and voluminous. Thimerosal dissociates in the body to ethyl mercury. The evidence for its reproductive toxicity includes severe mental retardation or malformations in human offspring who were poisoned when their mothers were exposed to ethyl mercury or thimerosal while pregnant, studies in animals demonstrating developmental toxicity after exposure to either ethyl mercury or thimerosal, and data showing interconversion to other forms of mercury that also clearly cause reproductive toxicity. The evidence for PMA comes from numerous findings of developmental toxicity in laboratory animals and interconversion data.

With regard to the second criterion, U.S. EPA, the authoritative body relied on when mercury and mercury compounds were listed under Proposition 65, currently identifies "mercury and mercury compounds" as causing reproductive toxicity. A chemical compound is a substance that consists of two or more chemical elements in union. The chemical symbol for mercury is Hg. Phenyl**mercury** acetate (PMA) has the chemical formula C_8-H_8-**Hg**-O_2. Thimerosal is a common synonym for ((o-carboxyphenyl)thio)ethyl**mercury**, sodium salt, which has the chemical formula C_9-H_9-**Hg**-O_2-S.Na (Register of Toxic Effects of Chemical Substances[3]). Thus, each is indisputably a mercury compound and as such is covered by this identification.

Multiple U.S. EPA documents clearly state that mercury and mercury compounds cause various types of reproductive toxicity, including developmental toxicity (which is a form of reproductive toxicity). This includes formal documents as well as informational materials available on the U.S. EPA's Web site. The formal U.S. EPA document published in 1994[4] meets the formal identification and scientific criteria in Section 12306 that would compel OEHHA to list mercury and mercury compounds, thereby listing thimerosal and phenylmercury acetate (PMA). A large report on mercury published by U.S. EPA in 1997[5] that reviewed developmental toxicity contains statements consistent with the 1994 U.S. EPA document. Therefore, because neither of the reconsideration criteria are met, and OEHHA finds the existing listing includes thimerosal and PMA as mercury compounds, OEHHA declines to refer thimerosal or PMA to the DART Identification Committee as requested in the Petition. This referral would only occur if either of the section 12306(j) criteria for reconsideration were met.

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[3] Database of the National Institute for Occupational Safety and Health, currently maintained by Elsevier Science, Inc.

[4] "Summary Review of Health Effects Associated with Mercuric Chloride: Health Issue Assessment," EPA/600/R-92/199, U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, 1994.

[5] "Mercury Study: Report to Congress," EPA 452/R-97-003, U.S. Environmental Protection Agency, Office of Air Quality and Standards and Office of Research and Development, December 1997.

With regard to the 1984 U.S. EPA document used as the basis for the initial listing of mercury and mercury compounds, OEHHA finds that the document formally identifies PMA as causing reproductive toxicity. OEHHA further notes that the document formally identifies inorganic mercury as causing developmental toxicity and, by discussing the biotransformation of alkylmercury compounds (i.e. thimerosal) to inorganic mercury, establishes that inorganic mercury is a metabolite of thimerosal and that it is therefore biologically plausible that thimerosal can cause adverse developmental effects. Further, other authoritative body documents, including the 1994 U.S. EPA report discussed above, would presently compel OEHHA to include thimerosal on the Proposition 65 list, were it not already on the list. Therefore, even if the initial listing of mercury compounds did not somehow support the inclusion of thimerosal and PMA as mercury compounds, other documents published since that time would compel the inclusion of the two chemicals on the list and it would be unjustifiable to remove them at this time.

While an exhaustive review of documents by other Proposition 65 authoritative bodies was not conducted, OEHHA notes that some of these other bodies describe mercury and mercury compounds as causing reproductive toxicity. For example, a rule by the U.S. Food and Drug Administration in 1998 clearly identifies PMA as causing reproductive toxicity within the meaning of Section 12306 and would compel the listing of PMA as causing reproductive toxicity under Proposition 65.

III. Background Concerning the Listing of Mercury and Mercury Compounds as Causing Reproductive Toxicity

Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code section 25249.5 et seq.), requires the Governor of California to publish a list of those chemicals known to the state to cause cancer or reproductive toxicity, and to revise and republish the list in light of additional knowledge at least once per year. A chemical is known to the state to cause cancer or reproductive toxicity if in the opinion of the state's qualified experts it has been clearly shown by scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity, or if a body considered to be authoritative by such experts has formally identified it as causing cancer or reproductive toxicity, or if an agency of state or federal government has formally required it to be labeled or identified as causing cancer or reproductive toxicity. For purposes of Proposition 65, there are five bodies recognized as authoritative for reproductive toxicity: the International Agency for Research on Cancer (IARC) solely as to transplacental carcinogenicity, the National Institute for Occupational Safety and Health (NIOSH), the National Toxicology Program (NTP) solely as to final reports of the NTP's Center for Evaluation of Risks to Human Reproduction, the U.S. Environmental Protection Agency and the U.S. Food and Drug Administration (FDA). (See Section 12306(l).)

On April 27, 1990, the California Health and Welfare Agency, at that time the designated lead agency for the implementation of Proposition 65, published in the *California Regulatory Notice Register (CRNR)* a Notice of Intent to List "mercury and mercury compounds" based on their identification by the U.S. EPA as chemicals causing reproductive toxicity, as required by Section 12306(i). The notice identified the 1984 U.S. EPA publication as the basis for the intended action. The notice invited objections to the proposed action to be delivered to the Health and Welfare Agency by June 1, 1990. No objections to or comments on the listing were received by the Health and Welfare Agency, and mercury and mercury compounds were subsequently added to the list effective July 1, 1990. A specific form of mercury, methyl mercury, had already been included on the Proposition 65 list since July 1, 1987. Methyl mercury was one of the first chemicals listed under Proposition 65 as causing reproductive (developmental) toxicity. It was added to the list on the basis of a finding by the state's qualified experts for Proposition 65, at that time the Proposition 65 Scientific Advisory Panel.

On October 29, 1996, Kerr Corporation[6] petitioned OEHHA to, among other things, remove mercury and mercury compounds from the Proposition 65 list, after Kerr Corporation had been sued earlier that year for allegedly failing to provide the clear and reasonable warnings required under Proposition 65. The Kerr Petition alleged that the listing of mercury and mercury compounds in 1990 was invalid because the specific document relied on for the listing referred to in the *CRNR* identified only methyl mercury as causing reproductive toxicity.

The Kerr Petition sought current and prospective removal of mercury and mercury compounds from the Proposition 65 list. Kerr sought relief pursuant to Section 12306(j), which would require OEHHA to determine that mercury and mercury compounds were no longer identified as causing cancer or reproductive toxicity by the authoritative body. Accordingly, in reviewing the Kerr Petition, OEHHA considered whether the listing was proper at that time. The review included a *CRNR* public request for[7] and receipt of scientific information on the reproductive and developmental toxicity of mercury and mercury compounds (excluding methyl mercury). On April 2, 1998, OEHHA denied the Kerr Petition finding that the current listing was proper, and further finding that more recent U.S. EPA documents "clearly would compel OEHHA to list mercury and mercury compounds."

In August 1998, Kerr Corporation filed an action for a peremptory writ of mandate to compel OEHHA to remove "mercury and mercury compounds" from the Proposition 65 list of chemicals known to cause reproductive toxicity (*Kerr Corporation v. Denton*, Sacramento County Superior Court No. 98CS01937). The court denied the petition on November 16, 1998. Kerr Corporation

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[6] "Petition to Remove 'Mercury and Mercury Compounds' from the List of Chemicals Identified as Causing Reproductive Toxicity," Kerr Corporation to the Office of Environmental Health Hazard Assessment, October 29, 1996.

[7] Request for Information on the Reproductive and Developmental Toxicity of Mercury and Mercury Compounds (excluding methyl mercury) *California Regulatory Notice Register,* March 28, 1997.

subsequently filed, then withdrew, an appeal of this decision. Consequently, OEHHA made no change to the listing of "mercury and mercury compounds," which continues to encompass elemental mercury, mercuric and mercurous ions and all compounds that contain mercury.

On October 15, 2003, Bayer Corporation petitioned OEHHA for reconsideration of "mercury and mercury compounds" to discern whether the listing encompasses thimerosal and PMA.

IV. Application of Section 12306(j) Reconsideration Criteria to Thimerosal and PMA

The criteria for OEHHA to apply in deciding whether to reconsider the determination that a chemical has been formally identified by an authoritative body as causing reproductive toxicity are contained in Section 12306(j), which provides that: "the lead agency shall reconsider its determination that the chemical has been formally identified as causing ... reproductive toxicity if the lead agency finds: (1) there is no substantial evidence that the criteria identified in ... [Section 12306] subsection (g) have been satisfied, or (2) the chemical is no longer identified as causing ... reproductive toxicity by the authoritative body." The Statement of Reasons for Section 12306 explains that the purpose of this regulation is to permit reconsideration of a listing where the Agency has listed a chemical in error and where the authoritative body relied on for the listing has changed its conclusion. As discussed below, neither the Section 12306(j)(1) or (2) criterion for reconsideration is met as applied to mercury and mercury compounds, including thimerosal and PMA.

A. The Section 12306(j)(1) criterion is not met because there is substantial evidence for the reproductive toxicity of thimerosal and PMA

A chemical listed under Proposition 65 via the authoritative bodies mechanism shall be reconsidered if there is no substantial evidence that the criteria for "as causing reproductive toxicity" have been satisfied. "As causing reproductive toxicity," means that either of the following criteria has been satisfied:

(1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or
(2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." (Section 12306(g).)

Below it is demonstrated that there is substantial evidence that both thimerosal and PMA cause reproductive toxicity, as defined in Section 12306(g).

Thimerosal

Upon administration of thimerosal, its metabolite ethyl mercury quickly dissociates from thiosalicylic acid and binds to blood or other tissue (IOM, 2001[8]). There are a number of studies providing direct evidence of developmental toxicity for thimerosal, ethylmercury and related mercury compounds. There are additional studies in laboratory animals showing interconversion of ethylmercury to other forms of mercury also demonstrated to cause developmental toxicity and other reproductive harm.

Use of thimerosal as a topical antibacterial was associated with increased risk of malformation in humans, and thimerosal has been shown to cause increased incidence of intrauterine death in rats when administered by injection, and in rabbits when administered intraoccularly (Heinonen et al., 1977; Gasset et al., 1975). In humans, accidental exposure to ethylmercury produced severe mental retardation in offspring, growth retardation, and decreased muscle tone (Bakulina, 1968). Related human data are from various poisoning incidents with ethylmercury and methylmercury, including prenatal poisoning. In animals, several studies have demonstrated developmental effects from ethylmercury, including decreased fetal body weight and crown-rump length in rats, preimplantation loss and fetal mortality in rats, reduced litter size in rats and cleft palate and growth retardation in mice (Bezbozhnaya, 1973; Chmielnicka et al., 1985; Clegg, 1971; Goncharuk, 1971). Ethylmercury in these studies is typically administered as ethylmercury chloride (also referred to as "ethyl mercuric chloride"), which readily dissociates to ethylmercury. In addition, human and animal data show the interconversion of ethylmercury to inorganic mercury (Clarkson, 2002; Fang and Fallin, 1973; Magos, 2003); inorganic mercury has been clearly shown to cause developmental toxicity. Ethylmercury has also been shown, like methylmercury, to accumulate in the brain and causes tissue damage (Magos et al., 1985). Taken together these studies indicate that the Title 22, Cal. Code of Regulations section 12306(g)(1) and (g)(2) criteria for listing under Proposition 65 are met for thimerosal. Some studies showing direct evidence of developmental toxicity of ethylmercury and thimerosal, as well as studies showing metabolism to other developmentally toxic forms of mercury, are listed below.

Bakulina AV (1968). The effect of a subacute granosan poisoning on the progeny. *Sov Med* 31(6):60-63.
This publication reports cases of prenatal poisoning from maternal ingestion of grain treated with ethylmercury. Neonatal symptoms included severe mental retardation, decreased birth weight and decreased muscle tone.

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[8] "Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders," Institute of Medicine, Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention, National Academy Press, Washington DC, 2001.

Chmielnicka J, Brzeznicka E, Baranski B, Sitarek K (1985). The effect of ethyl mercury on fetal development and some essential metals levels in fetuses and pregnant female rats. *Biol Trace Element Res* 8:181-189.

Chmielnicka et al. administered ethyl mercury chloride to pregnant rats at a dose of 2.5 mg Hg/kg/day by gavage every other day from gestation day 6 – gestation day 20 and did a standard fetal exam on gestation day 21. Group size was 14 pregnancies for the ethyl mercury experiment. Ethyl mercury had a significant effect on body weight gain of dams, fetal crown rump length and fetal body weight ($p<0.05$, litter basis).

Clarkson TW (2002). The Three Modern Faces of Mercury. *Env Hlth Perspect* 110(Suppl 1):11-23.
This paper reviews the toxicity and disposition of thimerosal in humans.

Fang SC and Fallon E (1973). Uptake, distribution, and metabolism of inhaled ethylmercuric chloride in the rat. *Arch Env Contam Toxicol* 1(4):347-361.
This paper reports on aspects of inhaled ethylmercury distribution and metabolism to inorganic mercury in the rat.

Goncharuk GA (1971). Experimental study of the effect of organomercury group pesticides on the generative function and progeny. *Gig. Sanit.* 36(7):87-91.
In pregnant rats exposed to ethyl mercury by inhalation, overall fetal death rate was 19.3% in controls and 42.8%. In rats treated orally with ethylmercuric chloride at 1/20 the LD50, the number of offspring per litter was smaller than in controls.

Gasset AR, Itoi M, Ishii Y, Ramer RM (1975). Teratogenicities of ophthalmic drugs. II. Teratogenicities and tissue accumulation of thimerosal. *Arch Ophthalmol* 93: 52-55.
Rats (n=10/group) were injected with 1.0 ml of 0.2% or 2.0% thimerosal i.p. from GD 6-18. Rabbits (n=7) were given 2 drops of 2% thimerosal in both eyes six times a day on gestation day 6 and four times a day on gestation days 7-18. An increase in intrauterine death was reported, with the incidence in rats being 1%, 14% and 36% in controls, 0.2% and 2.0% thimerosal groups, respectively. The incidence of in intrauterine death in rabbits was 15% in controls and 39% in thimerosal-treated animals.

Heinonen OP, Slone D, Shapiro S (1977). *Birth Defects and Drugs in Pregnancy.* Publishing Sciences Group, Inc., Littleton, MA.
Using data from the collaborative perinatal project, standardized relative risks for malformations between 2.04 and 3.13 were found for thiomersal (thimerosal). The authors concluded that "thiomersal, on the basis for extremely limited numbers (56 exposures) was associated with malformations overall, and with uniform malformations."

Magos L (2003). Neurotoxic character of thimerosal and the allometric extrapolation of adult clearance half-time to infants. *J Appl Toxicol* 23:263-269.
This paper reviews the clearance of thimerosal in humans, including its metabolism to inorganic mercury.

Magos L, Brown AW, Sparrow S, Bailey E, Snowden RT, Skipp WR (1985). The comparative toxicology of ethyl- and methylmercury. *Arch Toxicol* 57:260-267.
This paper reports on a study of the comparative distribution, toxicity and tissue histopathology in rats, including concentrations and effects in the brains of animals treated with the different mercury compounds.

Bezbozhnaya LP (1973). Embryotoxic and gonadotropic effects of ethylmercuric chloride on rats. *Tr Vses Nauch Issled Inst Vet Sanit [Transactions of the All-Union Scientific Research Institute of Veterinary Sanitation]* 46:157-163.
Findings were preimplantation mortality, fetotoxicity, fetal death, for maternal exposures. For paternal exposure, reduced weight gain in pups.

Clegg DJ (1971). Embryotoxicity of mercury compounds, *in: Special Symposium on Mercury in Man's Environment. Proc R Soc Can,* Ottawa Canada [page 141]. (as cited in Koos and Longo (1976). *Am J Obstet Gynecol* 126(3): 390-409).
Growth retardation resulted after a single application of a 40 mg/kg subcutaneous dose of ethylmercury on gestation day 10 to mice.

Morikawa N (1961). Pathological studies on inorganic mercury poisoning. II. Experimental production of congenital cerebellar atrophy by bis-ethyl-mercuric sulfide in cats. *Kumamoto Med.* 14:87.
In cats, application of 2-3 mg/kg daily through gestation produced ataxia and cerebellar hypoplasia.

Mandzhagaladze RN and Vashakidze VI (1972). Action of some chemical compounds on rat progeny and sex ratios. *Soobshch Akad Nauk Gruz SSR* 65:485-488.

PMA

Direct evidence of developmental toxicity for PMA [phenylmercuric acetate] comes from a number of experimental studies in animals, as indicated in the list below. Fetal mortality and resorptions were reported in studies in golden hamsters, rats, mice, rabbits and voles, and decreased birthweight in surviving offspring was reported in studies in golden hamsters, rats and mice (Chakurov and Todorov, 1985; Dzeirzawski, 1980; Gale and Ferm, 1971; Goncharuk, 1971; Hartke et al., 1976; Murakami et al., 1956). Additional evidence comes from data on interconversion of PMA to forms of mercury that are also known to cause developmental

toxicity, such as inorganic mercury (Gage, 1964; Miller et al., 1960). Thus, the Section 12306(g)(2) criteria for "as causing reproductive toxicity" are met for PMA, compelling its retention on the list.

Gale TF and Ferm VH (1971). Embryopathic effects of mercuric salts. *Life Sci.* 10(II):1341-1347.
Pregnant golden hamsters were injected intravenously with PMA at 5, 7.5, 8 or 10 mg/kg on day 8 of gestation. The incidence of resorbed (dead) fetuses in controls, 5, 7.5, 8 or 10 mg/kg dams was 4%, 0%, 28%, 34% and 88%, respectively.

Chakurov P and Todorov S (1985). Embryotoxic and teratogenic action of phenylmercuric acetate. *Veterinary Sci.* 23:30-34.
Pregnant female rats (6 per treatment group, 12 controls) were given PMA orally on days 4 and 5 or 3-19 of gestation. Total embryo-fetal mortality in controls and treated animals receiving PMA at 6.3 or 15.7 mg/kg on days 4 and 5 of gestation was 6.1%, 19.4% and 54.4%, respectively (not assessed in the group receiving PMA on days 3-19 of gestation). Mean birthweight in pups from control dams and dams receiving PMA on days 3-19 of gestation was 3.0±0.02g and 1.9±0.03g, respectively, that is, 37% lower birthweight for pups of dams treated with PMA compared to controls.

Dzeirzawski A (1980). Embryotoxic and teratogenic effects of phenyl mercury acetate and methyl mercury chloride in golden hamsters. *Polski Arch. Weterynaryjne* 22:263-287.
Pregnant golden hamsters, rats and mice were used in this study, and were administered various levels of PMA orally on varying days of gestation. While there was a relatively small effect on fetal survival in rats, the incidence of fetal resorptions in rabbits receiving 0 (control), 3 mg/kg or 5 mg/kg on each of gestation days 8, 10 and 12 was 2.5%, 17.6% and 31.0%, respectively, and in rabbits receiving 0 (control), 20 mg/kg on gestation days 8 or 5 or 30 mg/kg on gestation day 8 the incidence of fetal resorptions was 9.3%, 15.1%, 12.5% and 19.8%, respectively. Mean birthweight of surviving fetuses was also consistently reduced in a dose-related manner in all three species.

Gage JC (1964). Distribution and excretion of methyl and phenyl mercury salts. *Br J Ind Med* 21:197-202.
This study in rats showed that PMA is metabolized to inorganic mercury.

Goncharuk GA (1971) Experimental study of the effect of organomercury group pesticides on the generative function and progeny. *Gig. Sanit.* 36(7):87-91
This publication briefly described studies in which pregnant rats were exposed to organomercury pesticides by inhalation. The overall fetal death rate was between 8 and 19.3% in controls and between 10 and 28.1% for animals exposed to phenylmercury compounds, and fetal development was reported to be generally inhibited with reductions in fetal weight and length.

Hartke GT, Oehme FW, Leipold HW, Kruckenberg SM (1976). Embryonic susceptibility of *Microtus orchogaster* (common prairie vole) to phenyl mercuric acetate. *Toxicology* 6:281-287.
Pregnant voles received PMA by intraperitoneal injection at a wide range of doses on one of either days 8, 9 or 10 of gestation. The incidence of fetal mortality in dams receiving PMA on day 8 of gestation at 0 (control), 0.6, 0.125, 0.25, 0.5, 1, 2 or 5 mg/kg was 6%, 0%, 67%, 65%, 74%, 100%, 100%, 100%, respectively. Administration of the same doses on day 9 of gestation resulted in fetal mortality of 0%, 12%, 29%, 17%, 46%, 100%, 100%, 100%, respectively, and on day 10 of gestation 16%, 0%, 0%, 0%, 40%, 100%, 100%, 100%, respectively.

Miller VL, Klavano PA, Csonka E (1960). Absorption, distribution and excretion of phenylmercuric acetate. *Toxicol Appl Pharmacol* 2:344-352.
Rats and dogs administered PMA showed rapid metabolism of the PMA to inorganic mercury.

Murakami U, Kameyama Y, Kato T (1956). Effects of a vaginally applied contraceptive with phenylmercuric acetate upon developing embryos and their mother animals. *Ann. Rev. Res. Inst. Environ. Med. Nagoya University*. pp. 88-99.
Pregnant mice were exposed to approximately 0.1 mg of PMA intravaginally on day 7 of gestation or by subcutaneous injection on day 8 of gestation. The incidence of dead embryos on day 14 of gestation was 11.8% (control), 20.3% (day 7 gestation) and 24.2% (day 8 gestation), respectively.

B. The Section 12306(j)(2) criterion for reconsideration of the listing of mercury and mercury compounds is not met because the authoritative body, U.S. EPA, currently identifies mercury and mercury compounds as causing reproductive toxicity and thimerosal and PMA are mercury compounds.

Multiple U.S. EPA documents clearly state that mercury and mercury compounds cause various types of reproductive toxicity. This includes formal documents as well as informational materials available on the U.S. EPA's Web site. The formal U.S. EPA document published in 1994 meets the formal identification and scientific criteria in Section 12306 that would compel OEHHA to list mercury and mercury compounds, and thereby list thimerosal and PMA, were they not already listed under Proposition 65. A large report on mercury published by U.S. EPA in 1997 which reviewed developmental toxicity, a form of reproductive toxicity, contains statements consistent with the 1994 U.S. EPA document, but does not comprehensively review the evidence for the reproductive toxicity of the organomercury compounds besides methylmercury. Each of these documents is discussed below. They are presented in order of strength of support for the current authoritative body listing of thimerosal and PMA as mercury compounds.

1994 U.S. EPA Report

U.S. EPA, in its 1994 document, "*Summary Review of Health Effects Associated with Mercuric Chloride: Health Issue Assessment*," concludes that "[i]n both humans and experimental animals, mercury and its compounds may affect development and maturation of the female reproductive system; alter the function of the hypothalamus, pituitary, or reproductive organs; decrease ovulation and implantation; decrease male fertility; and cause teratogenic effects."[9] This statement and the document itself clearly and unambiguously meet the formal identification criteria for listing specified in Section 12306(d)(1) and (2); in that the document is a report published by the authoritative body which concludes that the chemicals cause reproductive toxicity, the document specifically and accurately identifies the chemicals, and the document has been reviewed in accordance with U.S. EPA policy and approved for publication. The statement is based on an evaluation of the evidence for reproductive and developmental toxicity of $HgCl_2$, in experimental animals and of the potential for other forms of mercury, including elemental and organic forms, to bioconvert to the inorganic ion, Hg^{2+}, a reproductive toxicant. With specific regard to PMA and thimerosal, the U.S. EPA document also cites a publication by Koos and Longo[10] that provides direct evidence of developmental toxicity in humans and animals for ethyl mercury, and of developmental toxicity in animals for PMA. A large body of evidence for the reproductive toxicity of other mercury compounds is also presented. Taken together, the evidence presented in the U.S. EPA 1994 document satisfies the listing criteria of Section 12306(g)(2). There are sufficient data to indicate that an association between adverse reproductive effects of mercury and mercury compounds (including thimerosal and PMA) in humans is biologically plausible.

It should also be noted that the modifier "may" in the U.S. EPA statement reflects that agency's stated position that chemicals causing developmental or reproductive toxicity will do so only under certain conditions, levels, periods and durations of exposure, and potentially only in some individuals within a population. It should not be interpreted as a reflection of uncertainty on the part of U.S. EPA about the potential for mercury and mercury compounds to cause reproductive toxicity. The 1991 U.S. EPA Guidelines for Developmental Toxicity Risk Assessment state that "... hazard identification for developmental toxicity and other noncancer health effects is usually done in conjunction with an evaluation of dose-response relationships, since the determination of a hazard is often dependent on whether a dose-response relationship is present. One advantage of this approach is that it reflects hazard within the context of dose, route, duration and timing of exposure, all of which are important in comparing the toxicity information available to potential human exposure scenarios. Secondly, this approach avoids labeling of chemicals as

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[9] The term "teratogenic effects" is sometimes used as a synonym for developmental toxicity, and on other occasions to describe specific manifestations of developmental toxicity, namely, major structural malformations, or birth defects.

[10] Koos BJ and Longo LD (1976). Mercury toxicity in the pregnant woman, fetus, and newborn infant. *Am J Obstet Gynecol* 126(3):390-409.

developmental toxicants on a purely qualitative basis." Furthermore, the 1996 U.S. EPA Guidelines for Reproductive Toxicity Risk Assessment state that "... in a population, background levels of toxic agents and preexisting conditions may increase the sensitivity of some individuals in the population. Thus, exposure to a toxic agent may result in an increased risk of adverse effects for some, but not necessarily all, individuals within the population."

1997 U.S. EPA Report

The statements in the 1994 U.S. EPA document are consistent with the statements in the most recent (1997) U.S. EPA document, "Mercury Study Report to Congress," which identifies the developing fetus as a primary target for developmental toxicity of mercury and mercury compounds: "The primary targets of mercury and mercury compounds are the nervous system, the kidney and the developing fetus." This document comprehensively reviews the health effects of elemental mercury, inorganic mercury and methyl mercury, concluding that they cause developmental toxicity. Besides methylmercury which is readily created in the environment from mercury releases from, for example, coal fired power plants, it does not comprehensively review developmental toxicity data on organomercury compounds, the environmental release of which has been severely limited by U.S. EPA's cancellation of pesticidal registrations beginning in the early 1970's for ethylmercury, PMA and the other organomercurials. Since the 1997 U.S. EPA document specifies that male and female reproductive toxicity of mercury and mercury compounds was not formally evaluated, the lack of statements in that document pertaining to those endpoints cannot be interpreted as inconsistent with the 1994 U.S. EPA document.

1984 U.S. EPA Document, "Mercury Health Effects Update. Health Issue Assessment"

The 1984 U.S. EPA mercury health assessment identified by the Health and Welfare Agency in its 1990 Notice of Intent to List mercury and mercury compounds was developed to review and evaluate the scientific information on the potential health effects from mercury exposure, with particular emphasis placed on those effects associated with human chronic inhalation exposures. The document includes a chapter on "Toxic Effects of Mercury in Man and Animals" which discusses the various acute, subacute and chronic health effects of mercury in humans and animals, including sections on "Vapor of Metallic Mercury" and "Other Forms of Mercury." In the latter section, there is a specific subsection on "Phenylmercury and related compounds."

The document also contains a chapter on "Pharmacokinetics and Biotransformation in Man and Animals," with sections on "Vapor of Metallic Mercury," "Compounds of Inorganic Mercury," "Methyl Mercury Compounds," and "Phenylmercury and Related Compounds." The chapter discusses these several forms of mercury, the bioavailability of which differs in several respects. Elemental (metallic) mercury can exist in the liquid or vapor phases, is readily absorbed as a vapor via the lungs but is very poorly absorbed via the gastrointestinal tract, and is distributed to the blood and tissues initially in the neutral valence state (Hg^0). Inorganic mercury compounds

dissociate initially into either the mercurous (Hg_2^{2+}) or mercuric (Hg^{2+}) ion, and are absorbed via the gastrointestinal tract in that form; the Hg_2^{2+} ion quickly goes to the Hg^{2+} form in blood and tissues. Organic forms of mercury such as methyl mercury and phenylmercury are absorbed as such via the gastrointestinal tract, and distribute to blood and tissues in that form. The document also discusses biotransformation of various forms of mercury, noting that they ultimately are metabolized to the mercuric ion (Hg^{2+}) and excreted in that form. With regard to PMA, the document states that "phenylmercury is rapidly metabolized to inorganic mercury." The document does not discuss the individual compound thimerosal, but states with regard to alkylmercury compounds (which include thimerosal) "an oxidation-reduction cycle for mercury exists in mammalian cells. ... The recently discovered cycle... is probably of profound importance in the toxicology of inorganic mercury. The oxidation-reduction cycle may also play a role in the metabolism of alkylmercury compounds. ... In short, it appears that inorganic mercury released into mammalian tissues by the demethylation of methyl mercury enters the oxidation-reduction cycle for inorganic mercury."

The 1984 document reviews in detail methyl mercury, which has been known to cause developmental toxicity in humans since the late 1950's, when severe brain damage in 22 infants around Minamata Bay in Japan was attributed to ingestion of methyl mercury by their mothers who consumed fish contaminated with the chemical during their pregnancies. Other human poisoning episodes and numerous experimental animal studies have confirmed the developmental toxicity of methyl mercury, and clarified that the developing nervous system is most susceptible to this chemical.

The 1984 U.S. EPA document also reviews the effects of exposure to elemental mercury, inorganic mercury compounds, methyl mercury compounds and phenylmercury (including phenylmercuric acetate or PMA) and related compounds on reproduction and development. The document contains several statements that relate to the potential for mercury and mercury compounds to cause developmental toxicity. Direct evidence for the potential for several forms of mercury to cause developmental toxicity is cited, as well as indirect evidence based on the metabolism of some forms of mercury to other forms known to cause developmental toxicity. Some statements made in the 1984 document by U.S. EPA are reproduced here.

> "phenylmercury is rapidly metabolized to inorganic mercury" (pp 4-30) and "most of the distribution and excretion patterns can be understood by the fact that phenylmercury compounds are rapidly broken down to inorganic mercury" (pp 4-33,34)
>
> "Mercury readily crosses the blood-brain and placental barriers...." (pp. 2-4)
> "Like other forms of mercury, methyl mercury readily crosses the blood-brain and placental barriers." (pp. 2-4)

> "Mercuric [inorganic] mercury is distributed via the bloodstream to all tissues in the body but penetrates the blood-brain and placental barriers to a much lesser extent (approximately ten times less) than mercury vapor." (pp. 2-5)
>
> "Parenteral administration of salts of inorganic mercury produce teratological abnormalities in experimental animals. Gale (1981) reported a variety of abnormalities including edema, retardation, ventral wall defects, pericardial cavity distention, cleft palate, hydrocephalus and heart defects in hamster fetuses given a single subcutaneous dose of mercury acetate (15 mg/kg) on the 8th day of gestation and killed on the 12th to 15th day. These findings confirm previous reports of experimental teratogenesis in hamsters given inorganic (mercuric acetate) and organic (phenylmercury acetate) compounds of mercury." (pp. 5-13)

In the 1984 U.S. EPA document, there is a statement in section 5.2.1 on the toxic effects of inorganic mercury compounds, that "[t]he human relevance of these experimental findings, in which highly toxic doses were delivered to animals via parenteral administration, is wholly unknown" (pp. 5-13). This statement qualifies the preceding statement that teratogenic effects of inorganic and organic compounds of mercury in animals are confirmed (see above). These statements pertain to the absence of data in humans indicating that there is a causal relationship between the chemical in question and reproductive toxicity. The relevant issue under the Proposition 65 regulations therefore becomes whether "[s]tudies in experimental animals indicate that there are sufficient data ... indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible." (Section 12306(g)(2)). The data cited in the 1984 document in support of the above-quoted statements indicate that such an association is biologically plausible for PMA. For thimerosal, the biological plausibility is supported by the discussion of the biotransformation of alkylmercury compounds to inorganic mercury, which the document identifies as causing teratological effects in experimental animals.

Because of these statements, and since the 1994 document by the same authoritative body identifies mercury compounds, inclusive of thimerosal and PMA, the chemicals do not meet the criteria for reconsideration pursuant to Section 12306(j)(2). The authoritative body still identifies the chemicals as causing reproductive toxicity, and, pursuant to Section 12306(j)(1), there is substantial evidence that each compound causes reproductive toxicity.

V. Findings by Other Authoritative Bodies

In addition to the documents noted above, various other formal documents and less formal informational materials developed by the U.S. EPA refer to mercury and mercury compounds as causing developmental toxicity, including documents published before and after the 1990 listing. There also are documents by authoritative bodies not involved in the original listing that refer to

mercury and mercury compounds as causing developmental toxicity. The existence of contemporaneous or subsequent documents published by an authoritative body not involved in an original listing that support the inclusion of an already-listed chemical on the Proposition 65 list impact OEHHA's decision regarding reconsideration of the previous listing, where the original basis for the listing is called into question. The Section 12306(d) and (g) criteria would need to be met by one or more of these documents. In such a case, to maintain the scientific integrity of the Proposition 65 list, OEHHA would then commence a process to change the stated basis for the listing.

An exhaustive search for and review of documents produced by other Proposition 65 authoritative bodies would be conducted if it appeared that the Section 12306(j)(2) criterion for reconsideration of a chemical was met. As shown above, this is not the case for thimerosal and PMA since the original listing authority still considers mercury compounds, which include thimerosal and PMA, to cause reproductive toxicity. Although an exhaustive search has not been conducted, OEHHA has identified several documents published by other authoritative bodies that refer to mercury and mercury compounds as developmental toxicants. For example, a final rule by the U.S. Food and Drug Administration in 1998 clearly identifies PMA as causing reproductive toxicity within the meaning of Section 12306. This would provide an independent basis for listing PMA as causing reproductive toxicity under Proposition 65. Some additional authoritative body documents are described in the Appendix to this response.

VI. Detailed Responses to Issues Raised in the Petition

The Petition makes a number of detailed arguments in support of its contentions. These are addressed in detail below. The responses to specific issues raised in the Petition follow the order of presentation in the Petition.

A. Petition section II. "Analysis A."

Petition: Pursuant to Title 22, Cal. Code of Regulations section 12306(j) any interested party may request that OEHHA reconsider its "determination that a chemical has been formally identified as causing cancer or reproductive harm" (Petition, page 2, paragraph 2).

Response: OEHHA agrees.

Petition: OEHHA must undertake the requested reconsideration, because the authoritative body never formally identified PMA and thimerosal as causing reproductive toxicity, per Title 22, Cal. Code of Regulations section 12306(j) (Petition, page 2, paragraph 3).

Response: The Petition is correct that the criteria for the lead agency to reconsider that determination are contained in Section 12306(j), which provides as follows:

> "[T]he lead agency shall reconsider its determination that the chemical has been formally identified as causing ... reproductive toxicity if the lead agency finds: (1) there is no substantial evidence that the criteria identified in ... [Section 12306] subsection (g) have been satisfied, or (2) the chemical is no longer identified as causing ... reproductive toxicity by the authoritative body."

PMA and thimerosal are mercury compounds and were therefore included in the 1990 listing of "mercury and mercury compounds." Thimerosal and PMA are chemicals that were determined by the lead agency for implementation of Proposition 65 to have been formally identified by an authoritative body as causing reproductive toxicity. OEHHA must only undertake reconsideration of this listing if one of the two criteria in Section 12306(j) are satisfied. Given that neither criterion is met, reconsideration of the mercury and mercury compounds listing is not required under this regulation.

Petition: Unless OEHHA clarifies that the present listing does not include thimerosal and PMA as mercury compounds, OEHHA is obliged to refer consideration of those chemicals to the DART Identification Committee for its recommendation concerning whether or not to separately list the chemicals (Petition, page 2, paragraph 3). If OEHHA does not interpret the "mercury and mercury compounds" listing to encompass thimerosal or PMA, full reconsideration is not necessary (Petition, page 2, paragraph 4).

Response: This is the reverse of the correct interpretation of the controlling regulation. The present listing of mercury and mercury compounds includes both thimerosal and PMA, since both are unequivocally mercury compounds. Since OEHHA will not reconsider the listing of thimerosal or PMA because the criteria in the regulation have not been met, the chemicals will not be referred to the DART Identification Committee. Conversely, had OEHHA determined that thimerosal and PMA should not be included in the present listing for mercury and mercury compounds, OEHHA would then be required to refer those two already-listed chemicals to the DART Identification Committee for a recommendation as to whether the chemicals should remain on the list.

B. Petition section "II. Analysis – B."

Petition: Title 22, Cal. Code of Regulations section 12306(j) requires reconsideration of a prior listing when a chemical is no longer identified as causing reproductive toxicity by an authoritative body. This provision also applies to situations where the original document supporting the listing actually did not formally identify a listed chemical. As indicated in the Final Statement of Reasons for Title 22, Cal. Code of Regulations section 12306(j), the regulation is intended to facilitate reconsideration "where the Agency has listed the chemical in error" (Petition, page 2, last paragraph).

Response: The complete quote from the Final Statement of Reasons for Section 12306(j), quoted in part in the Petition, is that "the purpose of this regulation is to permit reconsideration where the Agency has listed a chemical in error, and where the authoritative body itself has changed its conclusion." OEHHA agrees that the purpose of the regulation is to allow the lead agency an opportunity to correct situations where an error was made, or to update a listing where the authoritative body has changed its conclusion about the reproductive toxicity of a particular chemical.

OEHHA has concluded that the 1984 U.S. EPA report that formed the basis for the 1990 listing of mercury and mercury compounds meets the criteria for having formally identified PMA as causing reproductive toxicity. In the case of thimerosal, OEHHA believes that the document formally identifies inorganic mercury as causing developmental toxicity and, by discussing the biotransformation of alkylmercury compounds to inorganic mercury, establishes that inorganic mercury is a metabolite of thimerosal and that it is therefore biologically plausible that thimerosal can cause adverse developmental effects. In any case, however, the criteria for reconsideration of a listing, including a listing that was made in error, are clearly specified in Section 12306(j). The criterion that "the chemical is no longer identified as causing … reproductive toxicity by the authoritative body" requires that OEHHA consider the most current conclusions expressed by the authoritative body in publications that meet the criteria of Section 12306(d) for listing a given chemical. OEHHA has concluded that U.S. EPA continues to formally identify mercury and mercury compounds as causing reproductive toxicity and that the data cited by U.S. EPA in support of its current formal identification of mercury and mercury compounds as causing reproductive toxicity meets the criteria for listing a chemical under Proposition 65 with respect to both PMA and thimerosal. Therefore, U.S. EPA has not changed its conclusions concerning the reproductive toxicity of mercury and mercury compounds since the original listing decision was made.

With regard to the reconsideration criterion of section 12306(j)(1) that "there is no substantial evidence that the criteria for as causing reproductive toxicity identified in … [Section 12306] subsection (g) have been satisfied," OEHHA has determined that there is clear and substantial evidence that both PMA and thimerosal cause reproductive toxicity, as discussed above in section IV.A of this response.

Finally, as was noted in the Attorney General's successful arguments to the court in the case of *Kerr Corporation vs. Denton*[11] cited above, "Section 12306 is not a mechanism for reopening the old record. Rather, … it permits an ongoing challenge to the listing based on the current state of scientific evidence."

C. Formal identification under Proposition 65 – Petition section B.1

[11] *Kerr Corporation v. Denton*, Sacramento County Superior Court No. 98CS01937, Memorandum of Points and Authorities in Opposition to Petition for Peremptory Writ of Mandate, pp 14.

Petition: A "formal identification" requires an authoritative body statement that specifically and accurately identifies the chemical and concludes that 1) human studies indicate that the chemical causes reproductive toxicity, or 2) that reliable experimental animal studies indicate human reproductive toxicity is biologically plausible (Petition, page 3, first sentence; page 5, top).

Response: One of the ways a formal identification can occur is when an authoritative body report specifically and accurately identifies the chemical and concludes that the chemical causes reproductive toxicity. The term "as causing reproductive toxicity" is defined in Section 12306(g) as follows: "(1) Studies in humans indicated there is a causal relationship between the chemical and reproductive toxicity, or 2) studies in experimental animals indicate that there are sufficient data ... indicating that an association between adverse effects in humans and the toxin in question is biologically plausible." The petition is incorrect in stating that a "formal identification" requires that the authoritative body *conclude* that the criteria specified in Section 12306(g) have been met. Rather, as specified in Section 12306(c), it is the responsibility of OEHHA, as the lead agency for implementation of Proposition 65, to determine which chemicals have been formally identified by an authoritative body as causing reproductive toxicity. This includes a requirement that OEHHA evaluate the data cited by the authoritative body in support of its conclusion and determine that this is sufficient to meet the criteria for "as causing reproductive toxicity" specified in Section 12306(g).

Petition: The Scientific Advisory Panel at its meeting of April 14, 1989, considered the designation of U.S. EPA as an authoritative body under Proposition 65. Panel members did not want the authoritative bodies process compromised by unofficial stray statements or ambiguous references to classes of chemicals, such as "mercury compounds." Because of members' collective concern that designating U.S. EPA as an authoritative body would induce agency reliance upon any and all statements attributable to U.S. EPA, the Panel declined to identify U.S. EPA as authoritative at the April 1989 meeting. The Panel did not vote on the integrity-preserving motion concerning requisites for formal identification at the April 1989 meeting, and opted to avail itself the Health and Welfare Agency's expertise. The Agency then took the formal identification criteria, which the Panel had drafted specifically for U.S. EPA documents, and devised a generic regulation that could be used regardless of the authoritative body source. Bayer's Petition refers to a proposal by one member, Dr. North, and comments by various panel members regarding authoritative body designations. The Petition then cites the current regulations governing formal identification by an authoritative body (Title 22, Cal. Code of Regulations section 12306(d)). The Petition then notes that OEHHA has declined to list several chemicals that were listed under the U.S. EPA Toxic Release Inventory or in National Toxicology Program reports (Petition, pages 3-4).

Response: At their April 1989 meeting, there was a lengthy discussion among the Scientific Advisory Panel members of listing issues raised by authoritative body designations, along with

rather extensive input by some members of the public. Panel member Warner North moved for specific conditions to be attached to the U.S. EPA designation. After a lengthy discussion and proposals from the public, the state was asked by the Panel to draft conditions for authoritative body designation. (Dr. North: "The motion in my judgment requires further legal draftsmanship which has not been done. I see that as being the State's assignment to do that drafting." Transcript pages 140-141, April 6, 1989 Panel meeting.) The Panel then voted on a motion to provisionally accept U.S. EPA as an authoritative body, subject to conditions to be drafted for discussion at a future meeting. The motion passed. At their next meeting, held October 20, 1989, the Panel formally approved the designation of the U.S. EPA as an authoritative body, after having been informed of the provisions of the recently-adopted new regulation contained in Section 12306. In the intervening period between the two meetings, the state had drafted a proposed regulation and held a public hearing. Thus, the designation of the U.S. EPA as an authoritative body by the Panel was done in light of the conditions for authoritative body designation laid out in Section 12306.

It should also be noted that there has been a more recent decision by the state's qualified experts regarding the designation of U.S. EPA as an authoritative body for identifying chemicals as causing reproductive toxicity under Proposition 65. A public workshop on the authoritative bodies mechanism was held on June 11, 1998, which included specific reference to U.S. EPA identifications via the authoritative body mechanism. This was followed by a meeting on July 27, 1998 of the DART Identification Committee, the State's current qualified expert body with regard to reproductive toxicity. Similar issues to those discussed by the Scientific Advisory Panel previously in 1989 with regard to U.S. EPA as an authoritative body were raised and discussed again at these meetings and the DART Identification Committee was briefed on OEHHA's application of Section 12306. The DART Identification Committee subsequently unanimously reaffirmed U.S. EPA as an authoritative body, without qualification or limitation.

The Bayer Petition combines the Sections 12306(d) and (g) listing criteria, sometimes without distinguishing them. The Petition accurately quotes the listing criteria for "formally identified" as contained in section 12306(d), which by reference includes the definition "as causing reproductive toxicity" contained in section 12306(g). The distinction between the two sections is relevant to the Petition's examples of chemicals listed under the U.S. EPA Toxic Release Inventory or in National Toxicology Program reports but not added to the Proposition 65 list. The chemicals referred to in the Petition, which OEHHA declined to list, met the Section 12306(d) listing criteria for having been "formally identified" by the authoritative body, but did not meet either the listing criteria for "as causing reproductive toxicity" contained in Section 12306(g), or for the carcinogens discussed in the Petition, the criteria for "as causing cancer" contained in Section 12306(e).

Petition: As indicated by Dr. North's discussion of PCBs as "a class of substances in which there is ambiguity" for which the evidence may apply to some but not all members, "the State's

panel of experts did not envisage basing formal identifications on vague references to classes of chemicals like mercury compounds."

Response: Bayer is citing from statements by one member of the Panel in a discussion of the proposed listing of PCBs as carcinogens under Proposition 65. Bayer fails to note the subsequent listing of PCBs by that same Panel. The Petition also did not acknowledge that similar chemical class listings have been made by the state's qualified experts since the beginning of Proposition 65 implementation, nor did it acknowledge that the state's experts have not raised concerns regarding class listings via the authoritative bodies mechanism. Examples include similar class listings by that same expert panel prior to the 1990 addition of mercury and mercury compounds, including: the 1987 listing of beryllium and beryllium compounds, cadmium and cadmium compounds and nickel refinery dust; the 1988 listings of polybrominated biphenyls and polychlorinated biphenyls, aflatoxins, testosterone and its esters, tobacco smoke, alcoholic beverages, creosotes and crystalline silica; and the 1989 listings of chlorinated paraffins (60% chlorine) and radionuclides. PCBs were added to the Proposition 65 list by the panel in 1991 as known to cause reproductive toxicity. To date, a number of chemical classes have been listed under Proposition 65 via the authoritative bodies mechanism without substantive objection by the state's qualified experts. These experts are briefed on Proposition 65 listings via administrative mechanisms at each of their meetings, which must occur at least annually.

D. Identification of thimerosal – Petition section B.2

Petition: The 1984 U.S. EPA report on which the listing of mercury and mercury compounds was based "utterly fails to specifically and accurately identify thimerosal and PMA conclude (sic) that these chemicals cause reproductive toxicity" (Petition, page 5, bottom). The 1984 U.S. EPA report does not contain any specific mention of thimerosal, or a specific conclusion that thimerosal causes reproductive toxicity. The only oblique reference to thimerosal is that "methyl mercury and other short-chain alkyl mercurials primarily damage the central nervous system." Thimerosal is not a short-chain alkyl mercurial, and the only possible relevance is that one of the metabolites of thimerosal is a short-chain alkyl mercurial. Under Section 12306(g), even if the 1984 U.S. EPA report contained a valid conclusion that short-chain alkyl mercurials caused reproductive toxicity, it would still be necessary for OEHHA to determine that this conclusion was based on relevant, sufficient scientific studies (Petition, page 6, page 7 top).

Response: OEHHA agrees that the 1984 U.S. EPA document does not make specific mention of thimerosal, nor does it contain a specific conclusion that thimerosal causes reproductive toxicity. This is not the only relevant consideration, however. There are numerous examples under Proposition 65 where groups or classes of chemicals have been listed without each of the individual chemical compounds within the groups being identified (see above). Since thimerosal is not mentioned by name in the formal identification, the relevant issue is whether U.S. EPA

formally identified as causing reproductive toxicity a group of chemicals that includes thimerosal and whether the information cited in support of that formal identification meets the criteria of Section 12306(g).

The Petition states that one of the metabolites of thimerosal is a short-chain alkyl mercurial. Thimerosal is also commonly known as ethylmercury thiosalicylic acid sodium salt. Upon administration of thimerosal, its metabolite ethylmercury quickly dissociates from thiosalicylic acid and binds to blood or other tissue (IOM, 2001, as cited above). Thus, exposure to thimerosal directly results in exposure to ethylmercury, a short-chain alkyl mercurial. In instances where a chemical compound exerts its adverse reproductive effect through formation of a metabolic or dissociation product, data on that product can then be used to establish that the parent compound is known to cause reproductive toxicity. Thus, any conclusions relating to reproductive toxicity of ethyl mercury pertain to thimerosal (ethylmercury is a dissociation product of thimerosal). Further, any conclusions inclusive of short chain alkyl mercurials pertain to ethyl mercury.

Methyl mercury is a well-known human developmental toxicant that, as the U.S. EPA document correctly states, is primarily neurotoxic. The U.S. EPA document also states that "prenatal life is the most sensitive stage of the life cycle to methyl mercury," and cites sufficient data on developmental neurotoxicity to meet the requirements of Section 12306(g). Since susceptibility to the neurotoxicity of methyl mercury is greatest in the developing fetus, a conclusion equating the neurotoxicity of other short chain alkyl mercurials to that of methyl mercury can be viewed as a *de facto* conclusion that those other mercury compounds are also developmentally toxic. The U.S. EPA document also discusses biotransformation of alkylmercury compounds to inorganic mercury, which the document identifies as causing teratological effects in experimental animals.

OEHHA believes that all of the above could have provided an indirect basis for concluding that thimerosal was formally identified by U.S. EPA in its 1984 document as causing reproductive toxicity. If the original listing had been challenged in a timely manner, and if it had been established initially that the U.S. EPA document did not formally identify thimerosal, or a broader listing that included thimerosal, or that the data cited in the document in support of a conclusion that mercury and mercury compounds cause reproductive toxicity did not meet the criteria of Section 12306(g), the listing of organic mercury compounds (excluding PMA) might not have been based on that document. Alternative documents could have been considered at that time.

No such timely challenge was made to the listing, so the question becomes whether the current authoritative body listing is proper under the reconsideration criteria in the regulation (Section 12306(j)). Since the original authoritative body relied on for the listing (i.e., U.S. EPA) currently identifies mercury and mercury compounds as causing reproductive toxicity and the

current evidence cited by U.S. EPA meets the criteria for finding that mercury and mercury compounds (which include PMA and thimerosal) cause reproductive toxicity, the criteria requiring OEHHA to reconsider the listing of these chemicals are not met. The 1994 U.S. EPA document makes the identification consistent with the Section 12306(d) criteria and provides evidence sufficient within that document to satisfy the Section 12306(g) listing criteria for "as causing reproductive toxicity."

Tangentially, OEHHA notes that there were other authoritative body documents in existence in 1990 at the time of the listing of mercury and mercury compounds that could have been identified and considered if objections to use of the initial document had been raised.

As noted above, since thimerosal is currently on the Proposition 65 list as a mercury compound, and the Section 12306(j)(2) reconsideration criterion is not met for mercury compounds, the only other relevant regulatory standard concerning reconsideration is that contained in Section 12306(j)(1) as follows:

> "Subsequent to the addition of a chemical determined to have been formally identified by an authoritative body as causing ...reproductive toxicity to the list of chemicals known to the state to cause...reproductive toxicity, the lead agency shall reconsider its determination that the chemical has been formally identified as causing cancer or reproductive toxicity if the lead agency finds:
> (1) there is no substantial evidence that the criteria identified in [Section 12306] subsection...(g) have been satisfied."

In this case, the Section 12306(g) review of the evidence supporting listing under Proposition 65 goes beyond that contained in the U.S. EPA documents, identifying "mercury and mercury compounds" as causing reproductive toxicity. Section 12306(g) lays out the criteria for determining whether a chemical causes reproductive toxicity as follows: "(1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, or (2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of material toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible."

Looking at the larger body of evidence, OEHHA has determined that the criteria for "as causing reproductive toxicity" are met for thimerosal. There are human data on thimerosal and ethyl mercury as well as multiple studies in multiple species of laboratory rodents providing evidence of developmental toxicity. Thimerosal use as a topical antibacterial was associated with increased risk of malformation in humans (Heinonen et al., 1977), and thimerosal has been shown to cause increased incidence of intrauterine death in rats when administered by injection,

and in rabbits when administered intraoccularly (Gasset et al., 1975). Ethyl mercury has been shown to cause developmental toxicity in multiple animal species, including decreased fetal body weight and crown-rump length in rats (Chmielnicka et al., 1985), preimplantation loss and fetal mortality in rats (Bezbozhnaya, 1973), reduced litter size in rats following inhalation exposure (Goncharuk, 1971) and cleft palate and growth retardation in mice (Clegg, 1971). Similarly, an ethyl mercurial pesticide resulted in several cases of prenatal poisoning in humans including severe mental retardation and decreased birthweight after ingestion of treated grain (Bakulina, 1968). Thus, there is substantial evidence that the criteria for "as causing reproductive toxicity" identified in Section 12306(g) have been satisfied for thimerosal.

E. Identification of PMA – Petition section B.3

Petition: Although the 1984 U.S. EPA document specifically and accurately identifies PMA, it does not conclude that PMA causes reproductive toxicity within the meaning of Title 22, Cal. Code of Regulations section 12306(g) (Petition, page 7, point 3). U.S. EPA concluded that "it is not known whether phenylmercury compounds produce prenatal effects in humans." This statement eliminates the possibility that the criteria of Title 22, Cal. Code of Regulations section 12306(g)(1) were met. The Petition (page 8) then discusses the 1984 U.S. EPA document's discussion of developmental toxicity data for PMA in the context of the Title 22, Cal. Code of Regulations section 12306(g)(2) criteria, and concludes that this discussion does not constitute a conclusion that PMA causes reproductive toxicity, and that the reference to a single study does not meet the criteria of Title 22, Cal. Code of Regulations section 12306(g).

Response: OEHHA agrees that the statement in the 1984 U.S. EPA document noting the absence of data on prenatal effects of phenylmercury in humans eliminates consideration of the listing criterion of Section 12306(g)(1). Several other relevant statements and conclusions pertaining to PMA contained in the 1984 U.S. EPA document were not mentioned by the Petition, however. As noted above, in instances where a chemical compound exerts its adverse reproductive effects through formation of an active metabolite, data on the metabolite can be used to establish that the parent compound is known to cause reproductive toxicity. Thus, the statements that "phenylmercury is rapidly metabolized to inorganic mercury" (pp 4-30) and "most of the distribution and excretion patterns can be understood by the fact that phenylmercury compounds are rapidly broken down to inorganic mercury" (pp 4-33,34) support the subsequent conclusion that the teratogenic effects produced in experimental animals by administration of inorganic mercury salts *confirm* reports of teratogenesis in animals given PMA.

> "Parenteral administration of salts of inorganic mercury produce teratological abnormalities in experimental animals. Gale (1981) reported a variety of abnormalities including edema, retardation, ventral wall defects, pericardial cavity distention, cleft palate, hydrocephalus and heart defects in hamster fetuses given a single subcutaneous dose of mercury acetate (15 mg/kg) on the 8th day of gestation and killed on the 12th to

> 15th day. These findings confirm previous reports of experimental teratogenesis in hamsters given inorganic (mercuric acetate) and organic (phenylmercury acetate) compounds of mercury." (pp. 5-13)

The Petition's conclusion that the reference in the 1984 U.S. EPA document to only a single study of the reproductive toxicity of phenylmercury in and of itself means that the listing criteria of Section 12306(g)(2) have not been met is incorrect. A single study of sufficient quality can meet those criteria. However, in this case, the authoritative body (U.S. EPA) specifically identifies inorganic mercury as a metabolite of phenylmercury and also specifically concludes that studies of inorganic mercury demonstrating developmental toxicity confirm the developmental toxicity of PMA. Thus, multiple studies support the formal identification of PMA in the 1984 U.S. EPA document.

As with thimerosal, since PMA is currently included on the Proposition 65 list as a mercury compound, and since the U.S. EPA identified the chemical in the 1984 document and continues to identify mercury and mercury compounds as causing reproductive toxicity (within the meaning of Section 12306(g)), the reconsideration criterion of Section 12306(j)(2) is not met. The other reconsideration criterion –Section 12306(j)(1) (quoted above) – addresses the body of evidence pertaining to the reproductive toxicity of the chemical, including evidence not cited by EPA in the 1984 and subsequent reports. Looking at this larger body of evidence OEHHA has determined that the criteria for "as causing reproductive toxicity" are met for PMA, and the reconsideration criterion in Section 12306(j)(1) is not.

There are multiple studies of PMA in several species of laboratory rodents providing evidence of developmental toxicity, and together these studies meet the listing criteria for "as causing reproductive toxicity" in Section 12306(g). The incidence of fetal death was increased in a dose-related manner in pregnant golden hamsters injected with PMA (Gale and Ferm, 1971). In a study using oral administration of PMA to rats, mice and golden hamsters, mean birthweight of surviving fetuses was consistently reduced in a dose-related manner in all three species, and the incidence of fetal resorption was increased in rabbits (Dzeirzawski, 1980). Rats receiving PMA orally showed a dose-related increase in embryo-fetal mortality and a decrease in birthweight of surviving offspring (Chakurov and Todorov, 1985). A study using common prairie voles (*Microtus orchogaster*) demonstrated a dose-related increase in fetal mortality following intraperitoneal injection of PMA on various single days of gestation (Hartke et al., 1976). An early study in mice also showed increased incidence of dead embryos following intravaginal administration or subcutaneous injection of a contraceptive containing PMA on a single day of gestation (Murakami et al., 1956). Thus, there is substantial evidence that the criteria for "as causing reproductive toxicity" identified in Section 12306(g) have been satisfied for PMA.

F. Other authoritative body identifications – Petition section II.C

Petition: If OEHHA believes that other authoritative body documents formally identify thimerosal and PMA as reproductive toxins and wishes to expand the "mercury and mercury compounds" listing to encompass them, OEHHA must formally propose expansion of the listing.

Response: There is a fundamental error in the premise expressed in the Petition. The long-standing and current listing of mercury and mercury compounds unequivocally includes thimerosal and PMA, because all mercury compounds are included in the listing and thimerosal and PMA are indisputably mercury compounds. Thus, it is clearly impossible to "expand" the present listing to include thimerosal or PMA, or indeed any other mercury compound, since all are currently included.

Petition: Bayer's review of existing scientific literature has not uncovered any other authoritative body document that formally identifies either thimerosal and PMA as a reproductive toxin within the meaning of Title 22, Cal. Code of Regulations section 12306(g).

Response: While an exhaustive search was not conducted, OEHHA identified various authoritative body documents that contain conclusions relevant to identification of thimerosal, PMA and/or mercury compounds as reproductive toxicants as discussed above, and in the Appendix. Numerous authoritative body documents clearly demonstrate that mercury compounds in general, as well as specific subsets of mercury compounds including alkylmercurials and phenylmercurials, have long been and still are recognized as causing reproductive toxicity. Multiple authoritative body documents meet the listing criteria of Section 12306(g) and would compel the listing of PMA and thimerosal under Proposition 65 if they were not already included on the list.

Petition: The Petition also discusses in some detail what it considers to be OEHHA's analogous effort to expand the "nickel and certain nickel compounds" listing. In a footnote, the Petition also expresses the opinion that the propriety of all vague "and compounds" listings not accompanied by specific CAS numbers is in serious doubt.

Response: While this allegation is not relevant to the question concerning the "mercury and mercury compounds" listing as applied to thimerosal and PMA, the Petition is generally accurate in its factual description of the recent clarification of the 1989 listing of "nickel and certain nickel compounds," and of the proposed expansion of the listing to the all-encompassing "nickel compounds." The request by Bayer that OEHHA reconsider the listing of thimerosal and PMA is not analogous to the change to the "nickel and certain nickel compounds" listing, however. The original Proposition 65 listing of "nickel and *certain* nickel compounds" (emphasis added) clearly did not encompass all nickel compounds, but was ambiguous in that the "*certain* nickel compounds" were not individually identified. It should be noted that "nickel and certain nickel

compounds" were added to the Proposition 65 list as a result of a judicial decision interpreting Labor Code Section 6382(b)(1) and (d), which are incorporated by reference as Proposition 65 listing provisions pursuant to Health and Safety Code section 25249.8(a). However, the "certain nickel compounds" encompassed by the original listing were individually identified, and OEHHA modified the listing accordingly. This was not an expansion or contraction of the listing, but simply a clarification.

OEHHA's current proposed action to change the Proposition 65 listing to nickel and "nickel compounds" would indeed be an expansion of the current listing. This expansion will make the listing for nickel compounds exactly analogous to the current listing for mercury compounds. In contrast, the action proposed by Bayer for the current listing for mercury and mercury compounds, specifically to remove thimerosal and PMA from the listing, would be a *contraction* of the listing. The existing unqualified listing for mercury and mercury compounds is unambiguous by clearly and unequivocally including *all* mercury compounds (in contrast to the qualified listing for nickel and *certain* nickel compounds). Removal of thimerosal and PMA could in no way be viewed as simply a clarification of the scope of the original listing.

With regard to the Petition's stated opinions on the validity of what it alleges are "vague" listings of classes of chemicals such as mercury compounds without provision of Chemical Abstract Service (CAS) numbers, existing law requires that the list, report, or document relied on to support a listing decision specifically and accurately identifies the chemical. There is no requirement that a CAS number or numbers be provided for each chemical on the Proposition 65 list. Although OEHHA has made a practice of doing so, when appropriate, in the interest of facilitating use of the list by interested parties, there is no legal requirement to do so.

The listing for mercury compounds, the proposed listing for nickel compounds, and any other listing of that nature for an identifiable class of chemicals meets the requirements of Section 12306(d)(2) in that a compound that contains mercury or any other element so designated is specifically and accurately identified. A chemical compound is defined as "a substance that consists of two or more chemical elements in union" (Dorland's Medical Dictionary[12]) or "a substance containing two or more elements chemically combined in fixed proportions" (Webster's New World Dictionary[13]). If mercury is one of those elements, any resulting compound is a mercury compound. The chemical symbol for mercury is Hg. Phenyl**mercury** has the chemical formula C_8-H_8-**Hg**-O_2. Thimerosal is a common synonym for ((o-carboxyphenyl)thio)ethyl**mercury**, sodium salt, which has the chemical formula C_9-H_9-**Hg**-O_2-S.Na (Register of Toxic Effects of Chemical Substances[2]). Thus, by both scientific and common definition, each is indisputably a mercury compound.

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[12] Dorland's Illustrated Medical Dictionary, 27th Edition. W.B. Saunders Company, Philadelphia, PA
[13] Webster's New World Dictionary, Third College Edition. Simon & Schuster, New York, NY.

Petition: Regarding the Kerr Industries Petition in 1996, OEHHA was correct in identifying statements from the 1984 U.S. EPA document that pertained to formal identification, but erred in considering post-listing documents in determining that reconsideration of the listing was not warranted. It is necessary and appropriate to examine post-listing documents to ascertain whether an authoritative body continues to identify a chemical as a reproductive toxicant. However, the California Court of Appeal's decision (*Western Crop Protection Association et al. v. Gray Davis*, No. C029727 (Sup. Ct. No. 97CS02514)) makes it clear that where the issue is not whether a chemical continues to be formally identified, but rather whether it was ever formally identified, OEHHA cannot rely on documents referenced but not discussed by the authoritative body, much less upon documents published after the fact. This section of the Petition concludes by referring again to the proposed expansion of the listing for "nickel and certain nickel compounds," asserting that neither law nor logic tolerates post-hoc justifications for authoritative body listings.

Response: As noted above, subsequent to OEHHA's rejection of its Petition, Kerr Industries filed suit against OEHHA in Sacramento Superior Court (*Kerr Corporation v. Denton*, Case No. 98CS01937). Bayer's contention that OEHHA erred in considering post-listing documents in determining that reconsideration of the mercury and mercury compounds listing was not warranted is directly contradicted by arguments made successfully to the court in that case[14].

In the *Western Crop Protection Association et al. v. Gray Davis* case , the issue of reconsideration of a previously-listed chemical was not addressed. In ruling in OEHHA's favor, however, the Court of Appeal did note specifically that "Section 12306(i) provides a procedure by which a proposed listing by the OEHHA may be challenged on the ground 'there is no substantial evidence that the criteria' for listing have been satisfied," and that "[the plaintiff] did not avail itself of this procedure." This is directly relevant to the present Petition, since the selfsame procedure was available to the petitioner at the time the mercury and mercury compounds listing occurred, but was not employed by the petitioner. Internal documents obtained from Bayer by the Attorney General and provided to OEHHA demonstrate that as early as 1996 Bayer was well aware of the applicability of Proposition 65 to products containing thimerosal or PMA as preservatives, and that reformulation of such products with new preservatives was being considered (Enclosure 1. Bayer Internal Memorandum of January 30, 1997 re: Review of California's Prop 65 and Neo-Synephrine / Nasal Products). These documents also show that Bayer deleted its requirement for an odor test for thimerosal in certain products to eliminate the potential for analysts to be exposed to mercury via inhalation (Enclosure 2. Bayer Resource# 1989075, September 1998). Bayer had every opportunity to seek a clarification of the "mercury and mercury compound" listing in a timely manner but failed to do so.

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[14] Memorandum of Points and Authorities in Opposition to Petition for Peremptory Writ of Mandate, pp. 13-19

The clarification and proposed expansion of the listing for nickel and certain nickel compounds is in no way analogous to the requested removal of thimerosal and PMA from the Proposition 65 list as discussed above. As also noted above, the Petition has confused the mechanisms that resulted in the listing of "mercury and mercury compounds" (authoritative bodies mechanism) and "nickel and certain nickel compounds" (Labor Code mechanism), and their corresponding procedural requirements and constraints. These arguments are not relevant to Bayer's request for reconsideration of the "mercury and mercury compounds" listing as applied to thimerosal and PMA.

VII. Conclusion

OEHHA has carefully considered Bayer's Petition, which specifically seeks "to discern whether OEHHA interprets the 'mercury and mercury compounds' listing to encompass thimerosal and PMA [phenylmercuric acetate]." Bayer requested that if OEHHA interprets the "mercury and mercury compounds" listing to encompass thimerosal or PMA, the listing should be reconsidered. If OEHHA finds the converse, that the listing did not encompass thimerosal and PMA, then Bayer requested a clarification of the listing.

For the reasons discussed above, OEHHA finds that the 1984 U.S. EPA document identifies PMA as causing reproductive toxicity, pursuant to Section 12306(g). With regard to thimerosal OEHHA finds that the 1984 U.S. EPA document formally identifies inorganic mercury as causing developmental toxicity and, by discussing the biotransformation of alkylmercury compounds to inorganic mercury, establishes that inorganic mercury is a metabolite of thimerosal (which is metabolized to ethylmercury, an alkylmercury compound) and that it is therefore biologically plausible that thimerosal can cause adverse developmental effects.

The current listing under Proposition 65 is for "mercury and mercury compounds." PMA and thimerosal are mercury compounds, and therefore are listed as chemicals known to cause reproductive toxicity. The Petition requests in essence that OEHHA remove thimerosal and PMA from the Proposition 65 list of chemicals causing reproductive toxicity. In reviewing the Petition, OEHHA considered whether the listing is proper *at the present time*. Existing U.S. EPA documents clearly would compel OEHHA to list mercury and mercury compounds including thimerosal and PMA, therefore there is no justification for removing them from the Proposition 65 list.

The 1994 U.S. EPA document contains a clear and unambiguous statement that mercury and mercury compounds can cause developmental, male reproductive and female reproductive toxicity. It is supported by consistent statements about developmental toxicity of mercury and mercury compounds in the 1997 U.S. EPA document. There are no subsequent contradictory findings by the U.S. EPA, the authoritative body relied on for original listing, and thus U.S. EPA

currently identifies mercury compounds as causing reproductive toxicity and the 12306(j)(2) criterion for reconsideration is not met.

Had it appeared that reconsideration might have been appropriate, the findings of other authoritative bodies would have been evaluated before a final decision on reconsideration was made. As described elsewhere in this response, U.S. FDA documents contain clear and unambiguous statements that PMA and related mercury compounds are embryotoxic, and additional documents by other authoritative bodies conclude that mercury compounds cause reproductive toxicity. It is also clear that as early as 1971, U.S. EPA considered mercury compounds to cause reproductive toxicity in birds, and that the toxicity of all forms of mercury, and most especially alkyl mercury (e.g., ethyl mercury), led to the ban of such compounds in pesticides in the early 1970's.

Identification of mercury compounds as a class is clear, specific and unambiguous in that *any* chemical compound (i.e., any substance that consists of two or more chemical elements in union) that contains mercury is so identified. PMA and thimerosal are unquestionably substances that contain mercury in union with other elements. Current U.S. EPA documents clearly and specifically identify mercury compounds as causing reproductive toxicity. OEHHA therefore finds the listing of mercury and mercury compounds encompasses thimerosal and PMA.

Finally, there is substantial evidence from numerous scientific studies that thimerosal and PMA cause reproductive toxicity, and thus the Section 12306(j)(1) reconsideration criterion is not met for either chemical. Because reconsideration is not triggered, pursuant to Section 12306(j), the chemicals will not be referred to the DART Identification Committee for review as the Petition requested.

Based on its scientific review, OEHHA cannot make the findings requested by the Petition. Therefore, OEHHA denies Bayer's Petition for clarification that thimerosal and PMA are not covered by the listing of mercury and mercury compounds as chemicals known to the State of California to cause reproductive (developmental) toxicity.

VIII. Appendix: Authoritative Body Documents Addressing Mercury Compounds

Authoritative Body Documents Released Before 1990

Had any objections to the addition of mercury and mercury compounds to the list of chemicals known to the state to cause reproductive toxicity on the basis of the 1984 U.S. EPA document been raised at the time the listing action was taken, other relevant authoritative body documents that existed at that time would have been reviewed and potentially included in the deliberative process. Some other relevant documents published by authoritative bodies are identified below. Relevant statements contained in each document and a brief comment on the document are

provided below. These documents indicate that, prior to their listing under Proposition 65 in 1990, mercury and mercury compounds were considered by U.S. EPA and NIOSH to cause reproductive toxicity.

Authoritative Body: U.S. EPA
Title: Mercurial Pesticides, Man and the Environment
Date: 1971
Statements: "The recommendation of suspension of all alkylmercury-containing pesticides is based on the high toxicity of these compounds to humans." "the alkylmercuries ... are able to cross the placental barrier, where accumulation in the fetus may exceed that in maternal tissues and may cause fetal neurological damage."
Comment: This document is a staff report by the Special Pesticide Review Group of U.S. EPA, and represents a scientific and technical assessment of mercurial products registered with U.S. EPA for pest control purposes. This document in and of itself does not meet the criteria of 22 CCR 12306(d) since it indicates that its conclusions and recommendations are not a final action of U.S. EPA. However, U.S. EPA in 1971 (37 *Federal Register* 61, March 29) cancelled or suspended registration of alkylmercury-containing pesticides, referring in its order to "strong evidence that manmade mercury compounds and uses of mercury alter its natural distribution and form in a way to create a hazard over and above that posed by natural mercury. This concern caused the Agency to review all pesticidal uses of mercury, and two studies have now been completed." Thus, the recommendation for action in this document was subsequently implemented by U.S. EPA.

Authoritative Body: U.S. EPA
Title: Phenylmercuric Acetate Products: Determination and Order
Date: 1971 (36 *Federal Register* 202, October 19)
Statements: "Reproduction in birds is severely reduced by dietary exposure to mercurial compounds." "Methylmercury is teratogenic." "There is a greater risk of methylmercury poisoning to the fetus than to the mother."
Comment: This notice affirms the cancellation of registration of three phenylmercuric acetate products and orders the immediate suspension of their registration. Although the subject of the notice is specifically phenylmercuric acetate, it discusses toxicity of other forms of mercury because of the potential for phenylmercury to convert to those other forms.

Authoritative Body: NIOSH
Title: Occupational Health Guideline for Inorganic Mercury
Date: 1978 (September)
Statement: "Mercury, particularly organic forms, is known to adversely affect the fetus if the mother is exposed during pregnancy."
Comment: The document is identified as presenting a summary of pertinent information and data on mercury for employers, physicians, industrial hygienists, etc. The document was jointly

released by NIOSH, the Public Health Service, Centers for Disease Control and the Occupational Safety and Health Administration.

Authoritative Body: U.S. EPA
Title: Drinking Water Criteria Document for Inorganic Mercury
Date: 1988 (July)
Statements: "Unborn children and infants are more susceptible to the toxic effects of mercury than adults." "Fetal effects occur at lower blood concentrations of mercury than those causing maternal effects." "In the developing nervous system mercury has been shown to block normal growth by causing incomplete or abnormal migration of neurons, while other studies have shown that neuronal division is inhibited at critical stages of development."
Comment: The document reviews health effects of mercury exposure, and concludes that the fetus and infants are more susceptible to the toxic effects of mercury than are adults. Although the statements made are general, much of the information cited in support is for methyl mercury exposures. The document is an official U.S. EPA publication, which has been reviewed according to U.S. EPA peer and administrative review policies.

Two additional documents developed by NIOSH staff and U.S. EPA contractors also identify mercury and/or mercury compounds as causing developmental toxicity.

Authoritative Body: NIOSH
Title: Hazards from working with mercury in calibration laboratories
Date: 1980
Statement: "Effects on reproduction from exposure to other forms of mercury [in comparison to organic forms] are less well defined but there is convincing evidence in animals that inorganic mercury has a dose-related adverse pathologic effect on the developing fetus, with the production of congenital malformations."

Authoritative Body: U.S. EPA (Office of Water Regulations and Standards final contractor's report, reviewed by the Monitoring and Data Support Division of U.S. EPA.)
Title: An Exposure and Risk Assessment for Mercury
Date: 1981
Statements: "... mercury poses a particular hazard to the developing embryo." "In summation, elemental and methylmercury have been shown to readily cross the placenta, inducing a variety of developmental anomalies and fetal death." "The human fetus appears to be very susceptible to mercury poisoning."

Authoritative Body Documents Published After 1990

There are additional documents published by authoritative bodies subsequent to the date of addition of mercury and mercury compounds to the Proposition 65 list of chemicals known to cause reproductive toxicity that support the inclusion of these chemicals on the list. These documents are identified below, and a brief summary of relevant information and statements contained in each document is provided. As discussed above, conclusions in the first document provide a basis for listing PMA, and conclusions in the second document provide a basis for listing mercury and mercury compounds as causing reproductive and developmental toxicity, as defined in Title 22, Cal. Code of Regulations section 12306. Conclusions in the documents are based on scientific publications that predate the 1990 listing of mercury and mercury compounds.

Authoritative Body: U.S. FDA
Titles: Status of Certain Additional Over-the-Counter Drug Category II and III Active Ingredients. Final Rule [Docket Nos. 75N-183F, 75N-183D, and 80N-0280]. Vaginal Contraceptive Products for Over-the-Counter Human Uses; Establishment of a Monograph; Proposed Rulemaking [Docket No. 80N-0280]
Date: 1998 (63 Federal Register 77, April 22) and 1980 (45 Federal Register 82014, December 12)
Statement: "The Panel's primary concern regarding safety is related to the use of these ingredients during embryogenesis, pregnancy, and lactation and to their possible potential for fetal and neonatal damage. It is important to note that with the exception of mercury compounds, there is no evidence to date which would suggest that these ingredients under consideration have produced any such damage in the past." "Although phenylmercuric acetate (PMA) was the only mercury compound formally submitted for the Panel's review, compounds related to PMA, such as phenylmercuric nitrate (PMN), which also furnish mercuric ion, may be expected to have similar toxic properties and were therefore included generically in this discussion as mercury compounds. Therefore, it should be noted that in referring to data specifically related to PMA, it is the Panel's intention that such data be regarded as equally relevant for all related mercury compounds. Considering all of the data below, the Panel concluded that vaginal contraceptives containing mercury compounds as active ingredients are not safe." "The teratogenicity of PMA has been demonstrated in animal experiments." "Most importantly, PMA is embryotoxic." "PMA and mercuric acetate, as noted above, induce embryopathic effects in the golden hamster."
Comment: The Final Rule of April 22, 1998 refers to the Proposed Rule of December 12, 1980 as the basis for placing phenylmercuric acetate and phenylmercuric nitrate in Category II (not generally recognized as safe). Thus, although the formal identification meeting the requirements of Title 22, Cal. Code of Regulations section 12306(d) occurred in 1998, the authoritative body had formed its opinion 10 years prior to the Proposition 65 listing. The above statements are

quoted from the Proposed Rule, and are supported by data sufficient to meet the criteria of Title 22, Cal. Code of Regulations section 12306(g).

Authoritative Body: U.S. EPA
Title: Summary Review of Health Effects Associated with Mercuric Chloride: Health Issue Assessment
Date: 1994 (June)
Statements: "In both humans and experimental animals, mercury and its compounds may affect development and maturation of the female reproductive system; alter the function of the hypothalamus, pituitary, or reproductive organs; decrease ovulation and implantation; decrease male fertility; and cause teratogenic effects." "The disruption in placental function and ensuing embryotoxicity caused by both in vivo and in vitro exposure to $HgCl_2$ provide sufficient evidence to consider this agent as a developmental toxicant in experimental animals and a likely developmental toxicant in humans." "The chemistry of $HgCl_2$ must be considered in the context of mercury chemistry in general, as the various species of mercury (Hg^0, Hg^{2+}, Hg_2^{2+}, and organic mercury) are interchangeable in environmental or biological situations." "the mercury distribution in the blood ...may shift from a distribution characteristic of organic mercury compounds to one more suggestive of inorganic compounds."
Comment: The document reviews health effects of exposure to inorganic mercury to support actions taken on the basis of its identification as a toxic air contaminant. The document contains a clear and unambiguous statement that mercury and mercury compounds can cause developmental, male reproductive and female reproductive toxicity. The document cites studies of the reproductive and developmental toxicity of $HgCl_2$ and on the interconvertability of different species of mercury sufficient to meet the criteria specified in Title 22, Cal. Code of Regulations section 12306(g) with regard to the formal identification of mercury and mercury compounds as causing reproductive toxicity. The document is an official U.S. EPA publication, and has been reviewed according to U.S. EPA policies.

Authoritative Body: U.S. EPA
Title: Mercury Study Report to Congress Volume V: Health Effects of Mercury and Mercury Compounds
Date: 1997 (December)
Statements: "The primary targets of mercury and mercury compounds are the nervous system, the kidney and the developing fetus." "Elemental mercury is a developmental toxicant in experimental animals. If the mechanisms of action producing developmental toxicity in animals occur in humans, elemental mercury is very likely to produce developmental effects in exposed human populations."
Summary: The document is one volume in a comprehensive review of mercury. It reviews health effects of elemental mercury, inorganic mercury (mercuric chloride) and methyl mercury. The document also states that data suggest that inorganic mercury may cause human developmental toxicity, but that the data are currently insufficient for (quantitative) risk

assessment. The document states that U.S. EPA did not formally evaluate data on mercury for (male and female) reproductive effects.