Appendix A1

Response to Public Comments

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This document contains public comments and ARB staff response on the revised report entitled "Environmental Impact Assessment of tertiary-Butyl Acetate," released by the California Air Resources Board in June 2005. Comments were received from Daniel Pourreau of the Lyondell Chemical Company (Lyondell, July 30, 2005), Douglas Fratz of the Consumer Specialty Products Association (CSPA, August 1, 2005), and Jim Sell of the National Paint and Coatings Association (NPCA, August 1, 2005). The comments are paraphrased below with ARB and OEHHA staff response in italics.

Health Effects

Comment 1: The weight of the evidence indicates that TBAC and TBA are not genotoxic. The draft assessment speculates that TBA and, therefore, TBAC, might be genotoxic based on a single in vitro genotoxicity study with equivocal results. Attempts to repeat this single positive result in two GLP-compliant laboratories were unsuccessful. In contrast, numerous in vivo and in vitro genotoxicity studies for TBA (and for TBAC) are negative.

The report dismisses the TBAC genotoxicity data because it was obtained with DMSO as the carrier solvent. This is unjustified for several reasons. First, the scavenging property of DMSO is not an important factor in reducing sensitivity to either reactive oxygen species or aldehydes. Secondly, and contrary to the speculation in the report, the presence or absence of DMSO had no impact on mutagenic response of TBA in the studies reported by McGregor *et al*. (2005); it was not mutagenic in either case. If TBA was mutagenic and DMSO was the reason for the negative test, it would have produced a positive test in water. It did not.

Apart from the spurious result in Salmonella strain TA 102 reported by Williams-Hill (1999), all other assays of genotoxicity for TBAC or TBA cited in the CARB report are negative. The experimental evidence indicates that neither TBAC nor TBA is consistently positive in TA102 and both should be regarded as negative for genotoxicity in that strain as well. CARB and other regulatory agencies should, therefore, use a weight of the evidence approach regarding the genotoxicity data for TBAC and TBA and not use it to attempt to bolster weak carcinogenicity evidence. (CSPA and Lyondell)

Response: *The 2005 ARB TBAC report mentions the negative genotoxicity studies performed by NTP (1995) and Huntingdon Life Sciences Ltd. (2000a, b, and c). The available data suggest that TBA may not produce gene mutations or chromosomal damage due to bulky adduct formation. However, positive genotoxicity data for TBA have been reported by Tang et al. (1997) and Williams-Hill et al. (1999) suggesting that TBA may produce oxidative DNA damage.*

Tang et al. (1997) (cited by Budroe et al., 2004) examined the ability of TBA to induce DNA damage in human leukemia HL-60 cells using a Comet assay (single cell gel electrophoresis). TBA was not significantly cytotoxic at any of the

concentrations tested (1, 5, 10 and 30 mmol/L; 74, 371, 741 and 2224 µg/mL) as determined by lactate dehydrogenase (LDH) release. However, both the number of cells demonstrating DNA damage and the severity of damage increased significantly in a dose-responsive manner at all concentrations tested. This report was not available in an English translation for the 2002 and 2005 versions of the ARB TBAC report.

The report by Williams-Hill et al. (1999) was described in the 2005 ARB TBAC report. It should be noted that the description of the data from that study as "spurious" is disturbing, as it carries the implication that the manuscript lacks scientific integrity. This report demonstrates a statistically significant two-fold increase in TBA-induced revertants compared to controls. Several mutagens (formaldehyde, glutaraldehyde, cumene hydroperoxide, stannous chloride) which would not be expected to produce bulky adducts have been observed to produce a maximum approximately two-fold increase in revertants in Salmonella strain TA102 (Dillon et al., 1998; Pungartnik et al., 2005). This suggests that the two-fold increase in TA102 revertants after TBA exposure observed by Williams-Hill et al. (1999) is in fact biologically relevant. Williams-Hill et al. (1999) used water as the TBA carrier solvent. The Salmonella mutation studies done by Huntingdon Life Sciences Ltd. (2000b) used dimethyl sulfoxide (DMSO) as a carrier solvent. DMSO is well recognized as a free radical quencher, capable of reducing or eliminating mutagenic responses to chemicals that induce oxidative DNA damage (Fiala et al., 1987; Anwar et al., 1989; Zegura et al., 2004). The Lyondell comments cite a manuscript by McGregor et al. (2005). This manuscript states "DMSO is known to be a radical scavenger and so its presence at high concentrations might mask a mutagenic response due to oxidative changes". Therefore, it can be concluded that the statement by Lyondell that "the scavenging property of DMSO is not an important factor in reducing sensitivity to either reactive oxygen species or aldehydes" is inaccurate.

As discussed in the 2005 ARB TBAC report, the use of DMSO as a carrier solvent in the study by Huntingdon Life Sciences Ltd. (2000b) is sufficiently confounding that the results of this study should be considered inconclusive. The studies by McGregor et al. (2005) also suffer from this fault. These genotoxicity studies tested TBAC and TBA in one laboratory using Salmonella strain TA102 with a preincubation protocol, and TBA in a second laboratory using TA102 and a standard plate incorporation protocol. The TBAC and TBA study performed in the first laboratory was negative. However, the TBAC was dissolved in DMSO, rendering the results inconclusive. The authors stated that the TBA study was also negative. This study included test groups with TBA dissolved in water as well as TBA dissolved in DMSO, along with the appropriate solvent controls. Replicate experiments were performed. The results appear to indicate that TBA was positive for genotoxicity in the first experiment, and negative in the second experiment. This makes this study also inconclusive with regard to TBA genotoxicity.

After reviewing the above data, it can still be concluded that positive genotoxicity data exist for TBA.

Comment 2: The evidence for TBA carcinogenicity in animals is very limited and NTP did not find clear evidence of carcinogenicity in either rats or mice. (Lyondell and CSPA)

Response: *Oral TBA exposure has been demonstrated to induce renal tumors in male rats and thyroid follicular cell tumors in female mice (NTP, 1995). NTP (1995) classified the results of the two-year TBA drinking water cancer bioassay as providing "some evidence of carcinogenic activity of t-butyl alcohol in male F344/N rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female F344/N rats receiving 2.5, 5, or 10 mg/mL t-butyl alcohol. There was equivocal evidence of carcinogenic activity of t-butyl alcohol in male B6C3F$_1$ mice based on the marginally increased incidences of follicular cell adenoma or carcinoma (combined) of the thyroid gland. There was some evidence of carcinogenic activity of t-butyl alcohol in female B6C3F$_1$ mice based on increased incidences of follicular cell adenoma of the thyroid gland". These data are sufficient to conclude that TBA is an animal carcinogen, and may be considered to pose a potential cancer risk to humans.*

Comment 3: With respect to kidney tumors, the data meet all the criteria of the U.S. Environmental Protection Agency (USEPA) and the International Agency for Research on Cancer (IARC) for when such tumors should be disregarded for human health assessment because they are due to the alpha-2u-globulin mechanism, chronic progressive nephropathy (CPN), or a combination.

This draft assessment does not acknowledge that this is the opinion of Dr. Gordon Hard, a foremost expert in kidney toxicology and the alpha-2u-globulin mechanism. It also does not recognize a paper by Williams and Borghoff (2001) which reaches this conclusion. The draft assessment sets forth some arguments for why the alpha-2u-globulin criteria are not met. But, as explained in these comments, we believe those arguments are not scientifically accurate and do not overcome the strong data that clearly support an alpha-2u-globulin basis for the male rat kidney tumors.

The draft assessment points to female rat renal hyperplasia as an indication that the male tumors may not be due to the a2u mechanism. However, the report fails to acknowledge that these effects in the females occurred in a different part of the kidney and are part of advanced CPN, as Dr. Gordon has stated.

The slight increase in renal tumors in male rats exposed to TBA appears to be related to a2u, CPN, or a combination. Neither of these conditions occur in humans, thus, male rat kidney tumors from TBA exposure should not be used to infer human carcinogenicity from TBAC. (Lyondell)

Response: *The possibility that the male rat kidney tumors observed after oral TBA exposure may be related to an interaction between TBA and a2u-globulin (a2u) resulting in a2u nephropathy has been raised by Borghoff et al. (2001) and McGregor and Hard (2001).*

A criteria list for determining whether chemicals that induce male rat kidney tumors and may cause increased renal a2u production should be considered to be potential

human carcinogens has been defined in an International Agency for Research on Cancer (IARC) publication (Swenberg and Lehman-McKeeman, 1999). This criteria list is more rigorous than the criteria published by US EPA, and is probably more health protective.

The criteria published by IARC (Swenberg and Lehman-McKeeman, 1999) and referred to by Lyondell are as follows:

1. *Renal tumors occur only in male rats.*
2. *Acute exposure exacerbates hyaline droplet formation.*
3. *a2u accumulates in hyaline droplets.*
4. *Subchronic histopathological changes including granular cast formation and linear papillary mineralization.*
5. *Absence of hyaline droplets and characteristic histopathological changes in female rats and mice.*
6. *Negative for genotoxicity in a battery of tests.*

Additional supporting evidence could include:

1. *Reversible binding of chemical (or metabolites) to a2u.*
2. *Increased and sustained cell proliferation in P2 segment of proximal tubules in male rat kidneys.*
3. *Dose response relationship between hyaline droplet severity and renal tumor incidence.*

TBA fits some of these criteria; the NTP study (1995) demonstrated renal tumors only in male rats (Criteria 1) and described chronic histopathological changes including granular cast formation and linear papillary mineralization in male rats (Criteria 4). Acute and subchronic TBA exposure has been shown to exacerbate hyaline droplet formation in male rats (Criteria 2) (NTP, 1995; Borghoff et al., 2001). In the Borghoff et al. (2001) study, male and female F-344 rats were exposed by inhalation to 0, 250, 450, or 1750 ppm TBA 6 hours/day for 10 days to study a2u-nephropathy and renal cell proliferation and for 1 or 8 days to determine TBA levels in blood, liver and kidney following either single or repeated exposures. Neither accumulation of hyaline droplets in the kidney nor histopathological changes such as granular cast formation and linear papillary mineralization have been seen in either female rats or mice (Criteria 5). Reversible binding of TBA to a2u has been demonstrated (additional Criteria 1) (Williams and Borghoff, 2001), although a binding affinity was not determined.

Other criteria have not been completely met; a2u immunohistochemical staining was slightly greater in male rats exposed to TBA as compared to control male rats (Criteria 3) (Borghoff et al., 2001). However, the authors stated that no TBA exposure-related increase in a2u immunohistochemical staining intensity in male rats was noted. A significant increase in renal cytosol a2u concentrations as determined by an ELISA assay was noted in the male rat 1750 ppm group ($p < 0.05$) compared to controls, in contrast to the a2u immunohistochemical staining

evaluation, where no TBA exposure-related increase in staining intensity was noted. However, very little increase if any was noted in the 250 and 450 ppm groups. The renal a2u concentration in the 1750 ppm group compared to controls also appears to be substantially less than that observed for the a2u inducer TMP (Prescott-Matthews et al., 1997).

The dose response relationship between hyaline droplet severity and renal tumor incidence (additional Criteria 3) was not particularly strong in the NTP (1995) 13-week exposure study. Male rats exposed to TBA for 13 weeks developed increased hyaline droplet accumulation within renal tubule epithelium and lumens at all doses of TBA, but NTP stated that "Increased hyaline droplet accumulation was minimal" at the dose demonstrating a significantly increased tumor incidence (2.5 mg/ml). It should also be noted that the low dose (2.5 mg/ml) in the 13-week toxicity study was the high dose in the two-year cancer study. This suggests that hyaline droplet accumulations at the other doses causing increased tumor incidence would not be expected to be significant. Additionally, male rats in the 10 day TBA inhalation study by Borghoff et al. (2001) did not demonstrate significant increases in either hyaline droplet accumulation or renal a2u concentrations at estimated doses approximating those resulting in increased renal tumors in the 1995 NTP study.

Increased cell proliferation (measured by BrdU incorporation into replicative DNA) in the renal tubular epithelial cells of male rats exposed to TBA by inhalation was observed by Borghoff et al. (2001) (additional Criteria 2). However, the animals in this study were only exposed for 10 days. Therefore, no information is available from this study on whether cell proliferation was sustained chronically. Additionally, the increases in cell proliferation took place at TBA concentrations well below those producing increases in either hyaline droplet accumulation or renal a2u concentrations. In contrast, Takahashi et al. (1993) found significant increases in replicative DNA synthesis indicative of cell proliferation (measured by proliferating cell nuclear antigen (PCNA) staining) in the renal tubular epithelial cells of male rats exposed to TBA in drinking water at concentrations of 20 and 40 mg/ml for 13 weeks. The hypothetical progression of events leading from a2u nephropathy to renal tumors is that an accumulation of hyaline droplets containing a2u in the renal proximal tubules results in cell death, then compensatory cell proliferation, which leads to increased renal tumors. Swenberg and Lehman-McKeeman (1999) note that "dose related and male rat specific increases in cell proliferation have been demonstrated with all of the (a2u-inducing) chemicals evaluated, and the dose response relationships for cell proliferation parallel those for hyaline droplet formation and the induction of renal tumours". In the case of TBA, the data on the dose-response relationship between cell proliferation and hyaline droplet formation are conflicting. In the Borghoff et al. (2001) study, cell proliferation takes place at exposure levels where hyaline droplet formation is not increased, and would therefore not be expected to be causing cell death. Therefore, it is unclear whether cell proliferation is related to renal a2u concentration or hyaline droplet formation.

Finally, TBA does not fit Criteria 6 (negative for genotoxicity). TBA has been demonstrated to induce DNA damage in human leukemia HL-60 cells using a Comet assay (single cell gel electrophoresis) (Tang et al., 1997). Additionally, TBA

induces mutations in a Salmonella strain known to be sensitive to oxidative DNA damage (TA102) in the presence of rat liver S9 (Williams-Hill et al., 1999). The studies by Tang et al. (1997) and Williams-Hill et al. (1999) suggest that TBA may be genotoxic. These data, considered with the uncertainties associated with the ability of the assays used in the NTP (1995) genotoxicity studies to detect mutagenicity resulting from oxidative DNA damage, indicate that TBA should not be considered to be negative for genotoxicity. TBA therefore does not fit Criteria 6.

It should also be noted that adverse renal effects associated with TBA exposure have been observed in female rats. The severity of nephropathy was significantly increased in all TBA-exposed female rats in the NTP (1995) study, and this increased severity exhibited a dose-response. Renal inflammation was significantly increased in the 5 and 10 mg/ml female rat exposure groups, and significantly increased transitional epithelial hyperplasia was noted in the 10 mg/ml female rat exposure group. Both Huff (1996) and Melnick et al. (1997) noted that this nephrotoxic response in the female rat suggests the possibility of other processes leading to or influencing the kidney tumor response. Lyondell states in their comments that "Transitional cell hyperplasia develops when spontaneous CPN reaches advanced stages, as an integral part of that process. It occurs in advanced CPN in control rats as well as treated rats. It does NOT signify a toxic response to the chemical because it is an expected part of the late CPN process", and "As reported in the NTP study, exposure to TBA caused an exacerbation of CPN to advanced stages and was a contributor to mortality in TBA-treated animals". These two statements are logically inconsistent. If TBA is accelerating an adverse process resulting in greater mortality compared to controls, then this effect should be considered toxic.

The above data do not rule out the possibility of increased renal a2u concentrations playing a role in the increased renal tumor incidence seen in TBA-exposed male rats, either directly through the induction of nephropathy, or indirectly through increasing the TBA concentration in the kidney. The dissociation constant for TBA and a2u was not determined by Williams and Borghoff (2001). However, the dissociation constant for a2u and the related chemical MTBE (2.15 × 10-4 M) indicates that the binding affinity of a2u for MTBE is relatively weak (compared to the dissociation constant of 7.7 × 10-4 M for the high binding affinity chemical TMP). If the same is true for TBA, the possibility exists that dissociation of TBA from a2u may result in localized elevated concentrations of TBA in the renal proximal tubules.

As described above, 1) the dose response relationship between hyaline droplet severity and renal tumor incidence is weak; 2) conflicting data exist regarding the relationship between hyaline droplet formation and renal tubule cell proliferation. Increased cell proliferation has been observed at TBA doses where hyaline droplet concentrations are not increased, and therefore renal proximal tubule necrosis should not be occurring; 3) the existence of positive TBA genotoxicity data indicates that TBA should not be determined to be nongenotoxic; 4) TBA exposure has been demonstrated to cause adverse renal effects (nephropathy, inflammation, transitional epithelial hyperplasia) in female rats. In discussing the criteria for establishing the role of µ2u-globulin nephropathy in male rat renal carcinogenesis,

Swenberg and Lehman-McKeeman (1999) stated that "If clear evidence of renal toxicity or an increased incidence of renal tumours are observed in female rats or in other species, these criteria do not apply".

Animal tumor data should be considered to be relevant to the determination of human cancer risk unless clear and substantial mechanistic information exists indicating that such data is not relevant. In discussing the IARC mechanistic criteria for determining when male rat kidney tumors are not relevant to human cancer risk determinations, Swenberg and Lehman-McKeeman (1999) stated that "this is not a determination to be made lightly, and it is critical that the appropriate scientific evidence is developed to support the conclusion that a chemical does not pose a cancer risk to humans".

It is clear from the data described above that TBA does induce a µ2u-globulin nephropathy in male rats. However, these data also indicate that it would not be appropriate to determine that the increased renal tumors observed in TBA-exposed male rats are solely due to a2u-induced nephropathy. Therefore, the increased renal tumor incidences observed by NTP (1995) in TBA-exposed male rats should be considered suitable for use in human cancer risk assessment.

Comment 4: The available data support the hypothesis that the thyroid follicular cell tumors in mice are due to a threshold mechanism. While not enough tests have been conducted to demonstrate fulfillment of USEPA criteria for when such tumors should be treated as threshold, the existing data are consistent with a threshold mechanism. According to Dr. Michael McClain, a foremost expert in thyroid tumors, it is unlikely the thyroid tumors in female mice exposed to TBA are due to a genotoxic mode of action (indicating a likely threshold). (Lyondell)

Response: *Disruption of thyroid-pituitary homeostasis with elevation of TSH levels resulting in thyroid hypertrophy and hyperplasia has been associated with thyroid tumors in rodents. It has been suggested that rodents may be more sensitive to this carcinogenic mode of action than humans, and that modes of action may exist where a non-linear dose response may apply, or where the rodent tumor data may not be relevant to human cancer risk assessment (Hill et al., 1998). Mechanisms of thyroid-pituitary homeostasis disruption include 1) hepatic microsomal enzyme induction (primarily cytochrome P450) resulting in increased thyroid hormone metabolism and 2) a direct goitrogenic effect on the thyroid (Hill et al., 1989). Both mechanisms result in a compensatory increase in pituitary TSH with concomitant thyroid hyperplasia.*

However, the available mouse data do not support the involvement of increased thyroid hormone metabolism in mouse TBA carcinogenicity. There are no TBA cytochrome P450 induction data available for mice. McComb and Goldstein (1979) hypothesized that the increased TBA elimination rate observed in mice after chronic TBA exposure may be due to an increased conjugation of TBA, but did not publish any supporting data. Liver weights in mice exposed orally to TBA for 13 weeks (NTP, 1995) were only slightly increased in the 20 and 40 mg/mL male and 40 mg/mL female groups (115 and 107% of control for the male 20 and 40 mg/mL groups, respectively; 113% of control for the female 40 mg/mL group). Increased

relative liver weights may be due to cytochrome P450 induction, but may also be caused by other biochemical events (e.g., peroxisome proliferation).

The indirectly supporting evidence for cytochrome P450 induction in rats is weak. Bechtel and Cornish (1972) observed an approximate three-fold increase in acetanilide hydroxylase and aminopyrine demethylase activity in rats exposed to TBA either orally or by intraperitoneal injection. However, these data were contained in a meeting abstract and were not subsequently published in a peer-reviewed journal. Aarstad et al. (1985) noted in a meeting proceeding that inhalation exposure to 2000 ppm TBA for 3 days caused a small increase in cytochrome P450 activity in Sprague-Dawley rats (128% of control). A similar increase was not observed in rats exposed to 500 ppm for 5 days.

No data exist indicating that TBA results in increased thyroid stimulating hormone (TSH) or decreased thyroxine (T4) levels in either rats or mice. Additionally, NTP (1995) stated that no evidence of thyroid follicular cell hyperplasia was observed in mice exposed orally to TBA for 13 weeks. Such hyperplasia would be a likely outcome of altered TSH or T4 levels. NTP also did not observe liver hypertrophy or other evidence of enzyme induction. The above data indicate that TBA has not been demonstrated to significantly induce cytochrome P450, or alter TSH or T4 levels in mice.

It should be noted that US EPA has adopted the following science policy positions: 1) it is presumed that chemicals that produce rodent thyroid tumors may pose a carcinogenic hazard for the human thyroid, and 2) in the absence of chemical-specific data, humans and rodents are presumed to be equally sensitive to thyroid cancer due to thyroid-pituitary disruption (Hill et al., 1998). Also, a linear dose-response procedure should be assumed when needed experimental data to understand the cause of thyroid tumors are absent and the mode of action is unknown, or when the mode of action underlying thyroid tumors is judged to involve mutagenicity alone. Additionally, the existence of positive TBA genotoxicity data indicates that TBA should not be determined to be nongenotoxic.

Therefore, the above information indicates that TBA should not be considered to be a hormonally-mediated threshold carcinogen for risk assessment purposes, and that mouse thyroid follicular cell tumor data is relevant for use in determining the potential human cancer risk from TBA exposure.

Risk Assessment

Comments 5: The risk assessment uses conservative assumptions at every step in the analysis and therefore greatly overestimates the potential human health effects from use of TBAC. The quantitative cancer risk assessment for TBAC is overly conservative.

Lyondell and independent toxicology experts believe it is inappropriate to consider the TBA metabolite a non-threshold carcinogen at all. Thus, a linear extrapolation of risk is inappropriate. This conservative assumption is likely to overestimate the cancer risk of TBA by at least a factor of 10.

If a cancer potency factor is nevertheless calculated for TBA and TBAC, it should not be based on the male rat kidney tumors (as is the case in the draft assessment), because those tumors are not relevant for human risk assessment. Instead, it should be based on the female mouse thyroid tumors, which would further reduce the potency by a factor of 6.

Finally, the data do not support assuming, as does the draft assessment, that 100% of the inhaled TBAC will be converted to TBA. The data show that 26% of the inhaled TBAC is excreted to air and that the maximum conversion of the absorbed TBAC to TBA is about 45%. Therefore, the amount of inhaled TBAC converted to TBA would be only 33% and the cancer potency of TBAC would be further reduced by a factor of 3.

The cumulative effect of these conservative assumptions is to overestimate the CSF by a factor of at least 180. A more realistic, yet conservative, CSF would be on the order of 1.0 x 10-5 mg/kg-day-1 and a conservative inhalation unit risk factor for TBAC would be on the order of $2.9 \times 10^{-8} (\mu g/m^3)^{-1}$.

Finally, the report should acknowledge that, due to the low level of TBAC absorbed and metabolized to TBA, it would be virtually impossible to expose rats, mice or humans to sufficient quantities of TBAC to pose a cancer risk from TBA. Even short term exposure to the TBAC levels required to pose a potential cancer risk from TBA would be intolerable due to the odor, irritancy, and acute effects of TBAC at such high concentrations. (Lyondell and CSPA)

Response: *OEHHA generally uses non-threshold models to extrapolate to low-dose human cancer risk from animal carcinogenicity data, unless specific mechanistic data indicates this would not be appropriate. The existence of positive genotoxicity data for TBA indicates that the use of the above default cancer risk assessment procedure is appropriate. Also, as stated in detail in the responses to comments provided above, OEHHA believes that the increased renal tumor incidences observed by NTP (1995) in TBA-exposed male rats should be considered suitable for use in human cancer risk assessment and should be the basis for a cancer potency calculation since it was performed using the most sensitive species.*

The draft assessment does not make the assumption that 100% of the inhaled TBAC will be converted to TBA. The draft assessment assumes a 70% fractional absorption of TBAC, with 100% metabolic conversion to TBA. The fractional absorption factor is essentially equivalent to that observed by Huntingdon Life Sciences (2000) for rats (74%). Since no human pharmacokinetic data is available for TBAC conversion to TBA, the health-protective assumption was made that 100% of the absorbed TBAC would be metabolized to TBA.

Finally, since TBA is assumed to be a non-threshold carcinogen, exposure to TBAC at concentrations generating a TBA blood concentration less than that experienced by the exposed animals in the NTP (1995) studies would still result in an increased cancer risk proportional to the TBAC airborne concentration.

Comments 6: An appropriate acute REL would be much higher than 1000 $\mu g/m^3$. The draft assessment estimates that an acute reference exposure level (REL) for TBAC

would be an order of magnitude less than the acute RELs for solvents TBAC likely would replace (toluene, xylenes, methyl ethyl ketone (MEK)). This appears to be based on a value from a 1958 study that has not been replicated in more recent studies done according to Good Laboratory Practices. Using the more recent studies, the acute REL for TBAC would be equivalent to or greater than for toluene, xylenes, and MEK. This is consistent with occupational inhalation standards for these solvents. (Lyondell)

***Response**: An error was made in transforming units for the Industrial Biotest Laboratories (IBT) study. The suggested acute REL in the draft report derived from the IBT study should have been 10,000 µg/m^3, not 1000 µg/m^3. The corrections have been made in the final report.*

The acute REL of 10,000 µg/m^3 was derived from the 1958 study, which indicated a LOAEL of 5000 mg/m^3 for central nervous system effects. This study was done prior to the development of Good Laboratory Practice (GLP) standards, and therefore could not adhere to those standards. The GLP standards were developed to deter the possibility of falsified negative study data being submitted for regulatory purposes. Dropping positive study data from consideration solely because the study did not comply with GLP standards would not be health protective. Therefore, OEHHA chose the Industrial Biotest Laboratories (1958) data as the basis of an acute REL determination because it utilized the most sensitive species and strain. It furthermore cannot be assumed in the absence of human data that concentrations of TBAC producing acute human health effects will be similar to those concentrations of toluene, xylenes or methyl ethyl ketone demonstrated to produce acute human health effects.

Comment 7: Potential TBAC emissions are overestimated. Texanol™ and vinyl acetate are listed as solvents potentially replaced by TBAC. However, Texanol is used exclusively as a coalescent in water-based latex paints and cannot be replaced by TBAC. Vinyl acetate is a monomer used to produce vinyl polymers and is not used as a solvent at all. Lyondell believes that both chemicals should be removed from Table 2. On the other hand, TBAC is a potential replacement for trichloroethylene (TCE) in degreasing applications and TCE should be added to the list.

Lyondell believes that the substitution rates for the consumer, architectural coatings, and degreasing product categories are overestimated. TBAC is more expensive than most of the solvents it will replace. It also has a fairly rapid evaporation rate, a low flash point, and a strong odor. For these reasons, formulators will only use as much TBAC as they need to comply with mandated VOC content limits. Substitution rates for these product categories are likely to be no more than 25-75%. (Lyondell)

***Response:** The substitution scenarios are based on information supplied by the commenter and we believe are representative of TBAC's potential use in consumer products. While substitutions may be overestimated in some cases, from a risk manager's perspective, worst case scenarios must be considered. Based on survey data for automotive brake cleaners at one time, the perchloroethylene*

content in some automotive brake cleaners was as high as 98 percent by weight. Representing a plausible upper bound substitution estimate, we assumed that 100 percent of the perchloroethylene content would be replaced with TBAC. We also evaluated a moderate use scenario where TBAC would be substituted for xylenes and toluene. For architectural coatings, Table 3 states that the "percent of substitution" is 100%. This does not mean that 100% of all solvents listed in Table 2 would be replaced by TBAC. Instead, it means that ARB staff identified a limited number of solventborne architectural coating categories and a limited list of solvents that might be suitable for replacement with TBAC and then assumed that up to 100% of the those solvents could potentially be replaced by TBAC, under a worst-case scenario. This is reflected in Table 4 which shows that TBAC could potentially substitute for up to 61% of the xylenes, methyl ethyl ketone, and toluene being used in architectural coatings, well within the ranges that are recommended by Lyondell.

ARB's analysis did not assume that TBAC would be used as a drop-in replacement for Texanol in waterborne architectural coatings. The analysis assumed that some waterborne architectural coatings which contained Texanol could potentially be replaced by compliant solventborne coatings that contained TBAC. However, as explained in the first paragraph of Section 4.3, ARB's estimates for the potential use of TBAC (as shown in Table 3) only reflect substitutions for solventborne coatings. Therefore, ARB did not include replacement of Texanol-containing architectural coatings when quantifying ozone benefits in Table 3. Vinyl acetate was suggested as a potential chemical that can be replaced with TBAC. However, vinyl acetate has very limited use, as commented by Lyondell, so it was actually not included in the substitution analysis. Thus, vinyl acetate was removed from Table 2 in the final report. Regarding trichloroethylene, ARB staff did not identify any architectural coating applications where TCE was being used. For other categories, however, we will include trichloroethylene in future substitution analyses where appropriate.

We disagree with the assertion that TBAC's odor and expense will discourage manufacturers from using TBAC. Many formulators include additives to mask odor and we anticipate the price of TBAC will fall as economies of scale begin to develop.

Comment 8: The air quality modeling methodology includes several additional conservative assumptions. The draft assessment models potential human exposures on the basis of estimated outdoor concentrations. However, the majority of human exposures are due to indoor air, which would have lower concentrations of TBAC. CARB elsewhere has applied a factor of 0.70 to account for this. The same factor should be applied here.

The modeling of potential exposures of persons living near automotive brake shops and automotive body refinishing shops assumes that residences would be only 20 and 30 meters from the facility. Given the large facilities modeled, this is very unlikely. A distance of 100 meters would be a more appropriate, yet still conservative, assumption. The resulting exposure estimate would be about 30 percent of that derived by assuming a 20 or 30 meters distance.

The density of PERC is almost twice that of TBAC (1.62 g/ml vs. 0.87 g/ml). Hence, a can of degreaser will contain half as much TBAC as PERC on a weight basis. The degreasing efficiency of TBAC on axle and lithium grease is comparable to that of PERC. Hence, brake shop emissions and exposure levels will be approximately half those of PERC. The final report should take this into account when estimating potential TBAC occupational and near-source exposures from brake shops.

The report assumes that 100% of the xylene, toluene, and MEK used in auto refinish paints will be replaced by TBAC. For cost and performance reasons, this is highly unlikely. A substitution rate of 50% is a more reasonable assumption.

For emissions modeling purposes, CARB selected 50% large facilities emitting >2000 PPY (pound per year), 30% medium facilities emitting 1,000-2,000 PPY and 20% small facilities emitting less than 1000 PPY. In fact, the CEIDARS database shows that 90% of the facilities are small, 7% are medium, and only 4% are large. This results in an overestimation of either TBAC exposures from refinish facilities or of the number of people likely to be exposed to emissions from large facilities. The final report should either reduce the potential exposures of TBAC from these facilities or statistically correct the number of cases potentially resulting from these exposures. (CSPA and Lyondell)

Response: *Generic use of an indoor/outdoor factor is not appropriate in this case. For gaseous pollutants such as TBAC, ARB believes that, providing that there are not any indoor emissions sources, indoor concentrations are the same as outdoor. The screening health risk assessments are intended to be conservative estimates of the potential risk posed by a facility. Generally, the screening risk assessment uses conservative assumptions to estimate the potential cancer risk at the maximum point of impact. The article cited by the commenter is specifically addressing emissions from diesel engines. For the diesel particulate matter, a fraction of 0.70 is used to account for the gravity loss.*

The staff report explains that the modeling results are extrapolated from previous studies where the nearest off-site receptor may be either at the property line or at a minimum of 20 to 30 meters from the source. The property line is further than 20 meters for the larger facilities. The brake shop analysis included 13 facilities. For the larger brake shops, the minimum distance was larger, up to 330 meters for the largest facility. The automotive refinishing facility analysis included ten facilities where the largest facility had a minimum receptor distance of 80 meters.

The commenter inaccurately describes how ARB regulates consumer products and the TBAC substitution and exposure analysis. Consumer products are regulated using a "percent by weight" basis, as opposed to a "by weight base." As explained in the Staff Report, the exposure modeling scenarios used data from real "Brake Shop" facilities and assumed a drop-in (one-for-one replacement) for perchloroethylene, as suggested by the commenter. Therefore, our analysis is appropriate for characterizing potential exposures and risks due to potential substitutes of TBAC for perchloroethylene.

ARB did not assume that 100% of the xylene, toluene, and MEK used in auto refinish paints were replaced by TBAC. As stated in Section 5.3.3, ARB staff

assumed that emissions of toluene, xylenes, and MEK were substituted on one-for-two (50 percent) basis for TBAC, which is consistent with Lyondell's recommendation.

ARB staff agree that most facilities in CEIDAS are small (<1000 lbs/year). The modeling analysis is intended to serve as a screening analysis of a worse case scenario. Typically, we model the largest known facility. By modeling multiple facilities in each group we estimate a range of concentrations. Modeling a greater number of facilities with higher emissions enables us to generate a better estimate for the range of highest exposures. The estimates of cancer cases is derived from estimated ambient concentrations of TBAC (sec section 5.1.3 and 5.5) and the highest risk is derived from the concentrations modeled at the facilities. Therefore, the fact that a greater percentage of facilities modeled were greater does not result in an overestimate of the potential exposure.

Comment 9: Application of more reasonable assumptions would reduce the general population cancer risk estimate from TBAC usage from one in a million to less than 0.06 in a million and more likely less than one in a Billion.

For the automotive finishing facility scenario, the high end estimate would be reduced from 11 in a million to about 0.09 in a million, well below the level of concern. A more realistic cancer risk is on the order of 2 in a Billion.

For the brake shop scenario, the high end estimate would be reduced from 4 in a million to 0.07 in a million. A more realistic cancer risk from TBAC usage would be one in a billion. Subtracting the cancer risk from the replacement of PERC in brake cleaners, increased TBAC usage would result in 8 to 19 fewer cancer case cases. (Lyondell)

***Response**: In ARB's Draft Environmental Impact Assessment of tertiary-Butyl Acetate, it is estimated that a large body shop uses 3,000 gallons of automotive coatings per year, and assumes that the average amount of toluene, xylenes and MEK present in automotive coatings is 50 percent of the total VOC content of the coating. Under this worst-case scenario, a large automotive refinishing facility would emit more than 6,500 pounds per year of TBAC if TBAC was substituted for toluene, xylenes, and MEK on a one-for-one basis.*

Since the release of the draft report, the new 2002 Automotive Coatings Survey data has become available and the result suggests lower use (69%) of toluene, xylenes, and MEK than assumed previously. Accordingly, the maximum average ambient concentration of TBAC was revised to be 19.7 ug/m3, which corresponds to a health risk of eight excess lifetime cancer cases per million for the automotive refinishing facility scenario. For the brake shop scenario, the highest risk is four excess lifetime cancer cases per million.

It would not be meaningful to conclude that cancer risk would be reduced by substituting TBAC for perchloroethylene in brake cleaners. While we did base some potential TBAC-containing formulations on products that had contained perchloroethylene, its use had already been prohibited. As explained in the response to comment 7, these types of formulations were used to provide an upper-

bound for estimating risk. On April 7, 2000, the Board adopted the Airborne Toxic Control Measure (ATCM) for Emissions of Chlorinated Toxic Air Contaminants from Automotive Maintenance and Repair Activities. The ATCM prohibited the sale of automotive maintenance and repair products that contain perchloroethylene, methylene chloride, or trichloroethylene effective June 30, 2001, and prohibited the use of these products effective December 31, 2002. Because of these prohibitions, use of TBAC would result in increased cancer risk, as our analysis shows.

Comment 10: The health benefits associated with decreased usage of PERC, TCE, and MC should be considered. The cancer risk estimate for brake shops does not account for the cancer potency of PERC, the solvent TBAC would be replacing. Given that the cancer potency for PERC is at least 15 times and, more likely, 2,700 times greater than that used for TBAC in the draft assessment, a comparative analysis would show use of TBAC to reduce overall cancer risks for this scenario.

The decrease in cancer risk from replacing PERC in brake cleaners alone ranges from 8.1 to 19.4 fewer cases per one million. Even assuming that OEHHA is correct in its assessment of the cancer risk for TBA, replacing PERC with TBAC in brake cleaners would result in 7-10 fewer cancer cases per one million.

The cancer potency of TCE is at least 3 times and, more likely, 455 times greater than TBAC. TBAC is an excellent general purpose degreaser and is likely to replace TCE in some degreasing applications. CARB and other regulatory agencies should therefore consider the substitution potential of TCE for TBAC in solvent-based cleaners and the resulting decrease in potential cancer cases. (Lyondell)

***Response**: See response to comment 9. Because of the Board's action to prohibit the use of perchloroethylene, methylene chloride, and trichloroethylene, TBAC's use in these categories would likely result in an increased potential cancer risk, not a decrease as suggested by the commenter.*

Comment 11: The draft CARB assessment concludes based on information about likely uses of TBAC, that "the potential risk to the surface waters of the State is expected to be low." Lyondell agrees with this conclusion.

The draft assessment further states that the uncertainty associated with this conclusion is high, because "the toxicity of TBAC to a wide range of aquatic species is not known and information on exposure of aquatic species to TBAC in California through monitoring data is not available." Existing data do exist, however, that reduce that uncertainty.

As discussed in Lyondell's August 2001 submittal (p. 17), aquatic toxicity data in several species have been published for TBAC. LC_{50}, EC_{50}, or no effect concentration data are available for fathead minnows, *Daphnia*, a cryptomonad, a flagellate, a protozoan, a bacterium, two species of blue-green algae and one species of green algae. In all these species, TBAC showed low toxicity.

In addition, although water monitoring data are not available for TBAC, it can be predicted from the physical properties of TBAC that water concentrations would be quite low. TBAC has low solubility (1000 to 3000 ppm), and environmental fate

models show that TBAC partitions predominantly to air rather than to water (Webster and McKay, 1999; discussed at pp. 16-17 of the August 2001 Lyondell submittal).

Thus, existing data provide strong support for the conclusion of the draft CARB assessment that the potential risk to State waters from use of TBAC is low. Lyondell requests that the final assessment recognize this data which reduces the uncertainty associated with that conclusion.

Response: *Comments noted. The existing data on the potential risk to the California waters are limited and summarized in appendices C and F. The State Water Resources Control Board evaluated the existing data and concluded that the potential risk is expected to be low but its uncertainty is high.*

Comment 12: Lyondell believes that CARB should reevaluate the potential human health risk of TBAC usage in accordance with the following comments. CARB should rely less on cumulative conservative assumptions and give greater recognition to the weight of scientific evidence that indicates TBAC is unlikely to be a human carcinogen. A scientifically defensible, yet conservative, approach would be to use realistic numbers throughout the analysis and apply a 100-fold safety factor to the final number.

The final assessment should also acknowledge that TBAC is unlikely to pose significant health risks under realistic use and exposure scenarios. Even if CARB chooses to retain some of the conservative assumptions, the final assessment should recognize that actual risks are likely to be orders of magnitude below what is indicated by the use of multiple conservative assumptions and the analysis should include the health benefits that would result from decreased use of PERC, TCE, and MC, among others.

By greatly overstating the potential health hazards of TBAC and ignoring the health risks of the products it would likely replace, CARB may in fact discourage its use in cleaners and other product categories which contain more flammable, toxic, reactive and hazardous solvents. This could expose workers and the general population to higher ozone and TAC concentrations, resulting in a greater number of avoidable cancer cases from PERC, TCE, and MC and premature deaths and other adverse health effects from ozone.

We are dismayed at the continuing reservations about TBAC where, for example, the report states: “[S]taff will further evaluate appropriate consumer products categories that are most likely to use TBAC, to determine where or not use in these products could pose unacceptable exposures…” The report contemplates that individual air districts also may undertake such evaluations.

We believe that Lyondell has made a convincing case that OEHHA’s concerns about TBAC are not supported by the facts and that such a case-by-case approach will only serve to further delay the full, safe and effective use of TBAC in lower VOC products. (Lyondell)

Response: *See responses to comments 9 & 10. The California Environmental Quality Act (CEQA) requires ARB to identify the significant environmental impacts of*

proposed actions and to avoid or mitigate those impacts, if feasible. We also recognize the need to address neighborhood-scale air quality issues. Thus, it is incumbent upon the ARB to use conservative, "realistic worst case" scenarios to identify potential unacceptable near-source exposures and to mitigate those impacts. While our analysis does consider what we believe to be a "worst case" scenario, we have also included a typical use scenario, which results in a lower potential cancer risk.

Comment 13: Both manufacturers and the people of California will benefit from the TBAC exemption. We urge the Board to move forward with the exemption. (CSPA, Lyondell and NPCA)

Response: *Comment noted. Staff intends to propose the exemption of TBAC from the VOC definition in the California Consumer Products Regulation based on its low photochemical reactivity. However, staff will further evaluate appropriate consumer products categories that are most likely to use TBAC to determine whether or not use in these products could pose unacceptable exposures. If staff determines that the use of TBAC in certain products could cause unacceptable exposures, we will propose appropriate mitigation measures at the time the exemption is proposed.*

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