Appendix A2

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Comments on

"Environmental Health Impact Assessment of *tertiary*-Butyl Acetate (Draft)"

California Air Resources Board Staff Report (June 2005)

Lyondell Chemical Company
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INTRODUCTION AND SUMMARY

In November 2004, almost eight years after Lyondell's petition was submitted, the U.S. Environmental Protection Agency ("EPA") issued a Final Rule exempting TBAC from the definition of a volatile organic compound ("VOC") under title I of the Clean Air Act ("CAA"). The rule states that TBAC will not be counted as a VOC for purposes of VOC emission limitations or VOC content requirements but will continue to be a VOC for all recordkeeping, emissions reporting, and inventory requirements. *See* 69 Fed. Reg. 69,298 (Nov. 29, 2004), attached as Exhibit A. EPA's revision of the VOC definition was made on the basis that TBAC does not contribute appreciably to the formation of ground-level ozone. The Final Rule became effective on December 29, 2004.

Lyondell also submitted a petition to the California Air Resources Board (CARB) to exempt TBAC from the definition of volatile organic compound (VOC), based on TBAC's negligible ozone formation potential. With this petition, Lyondell submitted information on TBAC's toxicological and ecological properties. In a letter dated July 3, 2001, CARB requested additional toxicological and ecological information. In response, on August 27, 2001, Lyondell submitted to CARB a package of information ("Lyondell August 2001 submittal").

On March 26, 2002, CARB released its *Environmental Impact Assessment of Tertiary Butyl Acetate (Draft)* ("draft CARB assessment" or "draft assessment") and solicited comments on that draft from Lyondell. Lyondell provided detailed comments which are incorporated herein. We appreciate the opportunity to again comment on CARB's "revised draft assessment" published on June 30th, 2005.

The revised draft notes that granting a VOC exemption for TBAC would lead to some replacement of current solvents and would provide a number of benefits. It would result in a significant reduction of ground-level ozone concentrations and fewer premature deaths. The availability of a compound that would enable businesses to meet low VOC requirements would have positive economic impacts. The potential environmental and health impacts of TBAC use are expected to be low. Lyondell agrees with these aspects of the revised assessment.

The draft assessment also provides an estimate of the potential human health impacts of TBAC. In this latest draft, CARB has included an estimate of the health benefits associated with the reduction in ozone that would result from the replacement of reactive VOCs with TBAC. These health benefits are significant, with an estimated 770 fewer premature deaths statewide over a 70-year period. These health benefits far outweigh the estimated health risk from exposure to TBAC, even when these risks are greatly overestimated as they are in the draft report.

As with the first draft assessment, Lyondell believes that this revised draft report still incorporates a number of excessively conservative assumptions and that it does not provide a balanced perspective on the health risk/benefit of increased TBAC usage. For example, the draft assessment assumes that TBAC may pose a risk of human cancer, based on rodent cancer data for *tertiary*-butyl alcohol (TBA), a metabolite of TBAC. However, the draft assessment still

does not provide information that would enable the reader to recognize how very limited the animal carcinogenicity data are.

The report then makes several more conservative assumptions regarding the cancer slope factor and the amount of TBAC absorbed and metabolized to TBA. Taken individually, these conservative assumptions may appear reasonable and appropriately protective of human health. However, taken collectively, the cumulative effect of these worst case assumptions is to overestimate the potential cancer risk for TBAC by a factor of at least 180.

Compounding this overestimation of the cancer risk, the draft assessment makes several worst case assumptions when estimating population-weighted and near source exposures. The net result is that the health risks associated with TBAC are overestimated by several orders of magnitude.

Furthermore, no attempt is made to estimate the health benefits resulting from the replacement of Toxic Air Contaminants (TACs) such as PERC, Methylene chloride (MC), and trichloroethylene (TCE), whose cancer potency factors are multiples of that postulated for TBAC. The report mentions that replacing these solvents with TBAC could result in an increase in ozone but fails to discuss the significant reduction in cancer risk that would also result from these substitutions.

Based on CARB's analysis in Appendix H, the cancer risk associated with the use of PERC in brake cleaners alone ranges from 8.1 to 19.4 cancer cases per one million. Even if OEHHA's analysis of the potential health risks from TBAC was correct, using it instead of PERC and other solvents would result in ***7-10 fewer cancer cases per one million***, not the 1-12 potential additional cases the report estimates. As is the case with ozone formation, a balanced analysis of the health impact of increased usage of TBAC should not exaggerate its potential health risks and must take into account the health benefits that would result from decreased usage of more hazardous solvents such as PERC.

These comments make the following points concerning the health risk assessment of the draft CARB assessment.

- **The revised draft assessment still treats TBAC as being a potential carcinogen. However, the available data indicate this likely is not so.**
    - **Genotoxicity:**
        - There is no credible evidence that TBA or TBAC are 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. For these reasons, the negative genotoxicity data for TBAC obtained with DMSO with several *Salmonella* strains should be considered and CARB should acknowledge that the speculation that it may be genotoxic because TBA may be genotoxic is not supported by the weight of the evidence.

- 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.

- **Carcinogenicity:**

  - There is no direct evidence of TBAC carcinogenicity. The cancer concern is based on a National Toxicology Program (NTP) study of the TBA metabolite that was administered to rats and mice (NTP, 1995).

  - The evidence of TBA carcinogenicity in rats and mice is weak.
    - NTP did not find clear evidence of carcinogenicity in either rats or mice.
    - There was no increase in tumors in rats when examined by the standard protocol. Upon taking extra sections of kidney from male rats, there was an increase in kidney tumors at the mid-dose only. However, no historical control data were presented for kidney tumors in studies with step sectioning. Thus the tumor response in male rats exposed to TBA was either extremely weak or non-existent, and the incidence in control male rats indicates these are not as rare as suggested in the draft report.
    - Thyroid tumors showed a small but statistically significant increase only in high-dose female mice. There was no statistically significant response at any of the lower doses. OEHHA should acknowledge that, if this is due to a carcinogenic response to TBA, it is a very weak response consistent with a threshold mechanism. The report should also note that it would be virtually impossible to elicit that response from TBAC exposure, since mice would have to be exposed to sustained TBAC concentrations on the order of 4,500 ppm to produce the high-dose TBA level of the study. This level of exposure exceeds the maximum tolerated dose for mice.

  - There is strong evidence that the male rat kidney tumors are not relevant to humans.
    - 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 α2u 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 α2u, 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.

➢ The available data indicate that the thyroid tumors in the female mice are due to a threshold mechanism for TBA.

- 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).

- **The draft assessment greatly overstates the potential health risks for TBAC because of its reliance on multiple conservative assumptions, both for the hazard and on the exposure elements.**
  - Overestimation of the cancer risk
    - ➢ 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 x 10^{-8}(µg/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.**

- Overestimation of TBAC exposures
  - Lyondell believes that 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.
    - We believe 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%.
  - 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, 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.

- 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.**
- 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.

- Like the solvents it would replace, TBAC can be handled safely and responsibly. Furthermore, replacement of PERC, TCE, and MC by TBAC would provide health benefits.

- **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 therefore 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.

I. THE AVAILABLE DATA INDICATE THAT TBAC IS UNLIKELY TO POSE A HUMAN CANCER HAZARD

The available evidence indicates that TBAC is a low toxicity chemical. As stated in the draft CARB assessment, "TBAC has low acute inhalation, oral, dermal, and ocular toxicity and no impacts in several short-term genotoxicity assays." (p. 4)

No carcinogenicity study has been conducted on TBAC, although, as noted in the draft assessment, several genotoxicity studies have been conducted and are negative. The draft assessment focuses on the potential carcinogenicity of a metabolite of TBAC – *tertiary*-butyl alcohol (TBA) – and assigns a cancer potency to TBAC based on the TBA data.

The OEHHA decision to treat TBAC as a potential carcinogen has three elements: 1) a single spurious positive *in vitro* genotoxicity test using TBA; 2) observation of kidney tumors in high-dose male rats exposed to TBA; and 3) observation of follicular thyroid cell tumors in high dose female mice exposed to TBA. The following discusses the lack of strength in each of these elements.

Even for TBA, however, the evidence for potential carcinogenicity is quite limited. In rodents, only minor increases in tumors were observed in treated animals. Furthermore, the evidence strongly indicates that the kidney tumors observed in rodents exposed to TBA are due to mechanisms not relevant to humans, and that the thyroid follicular cell tumors are due to a threshold mechanism, indicating that a linear extrapolation model for the cancer potency is inappropriate.

Yet further, pharmacokinetic data indicate that it would be impossible to expose rodents and, by inference, humans to sufficient TBAC to cause increased tumors from the TBA metabolite.[1] Thus, the available data indicate that it is unlikely that a cancer study for TBAC would be positive and demonstrate that human carcinogenicity from anticipated TBAC exposures is highly unlikely.

A. The weight of the evidence indicates that TBAC and TBA are not genotoxic

As summarized in both the draft CARB assessment and Lyondell's toxicity summary, both TBAC and TBA have been subjected to a number of *in vivo* and *in vitro* genotoxicity studies. The results have consistently been negative, with one exception. The exception involves an *in vitro* assay of TBA with *Salmonella* strain TA102, a strain designed to detect oxidative DNA damage (Williams-Hill et al., 1999). The draft CARB assessment focuses

[1] Because of TBAC's low solubility in water, it is not possible to conduct a drinking water carcinogenicity study. For an inhalation study, to attain TBA concentrations that would cause tumors, the TBAC concentrations would have to be at levels that would be lethal. *See* Section II.A.2.

on this one positive test as evidence of the potential for TBA (and, thus, TBAC) to cause cancer. However, the significance of this one test is doubtful for the following reasons:

1) It is questionable whether the test is positive in the first place

Generally, for a *Salmonella*/mammalian mutation assay (or Ames assay) to be considered positive, the number of mutations in the treated sample must be at least double those in the control. In this case, the number of mutations in the treated sample was not quite twice those of the control. In addition, the authors noted that, for the test system to be considered stable, the number of mutations in the control should be within 200 to 400. In this case however, the number of mutations in the control exceeded 400. Thus, it is questionable whether this test should be treated as a positive – at the most, it is equivocal.

2) A second test performed under GLP conditions was negative

Lyondell sponsored a second TA102 test of TBA, which was negative (HLS, 2000a). Thus, even if the first test is considered positive, that result was not reproducible. In addition, TBAC was negative in the TA102 test (HLS, 2000a).

The draft CARB assessment (p. 20) discounts the repeat of the TA102 test on the basis that the TBA was dissolved in DMSO.[2] The draft assessment asserts that DMSO is a free radical scavenger and easily penetrates cell membranes. The implication of this assertion is that the DMSO prevented the TA102 assay from being positive. However, DMSO is commonly used as a solvent in *Salmonella* (Ames) assays, including assays using strain TA102, and the influence of DMSO on the mutagenic potency of some chemicals has been studied. No cases have been found where a material was mutagenic in strain TA102 in the absence of DMSO, but not mutagenic in the presence of DMSO. In a few studies, DMSO diminished the potency or intensity of the mutagenic response, but did not eliminate it (Fiala et al., 1987; Faux et al., 1994; Hubner et al., 1997). While the first two articles discuss the generation of active oxygen and DMSO as an oxygen scavenger as the reason for diminished activity, Hubner et al. (1997) assert that DMSO, along with ethanol and diethyldithiocarbamate, reduces the mutagenicity of ethylcarbamate in TA102 because it inhibits CYP2E1, the enzyme responsible for generating the active mutagen from ethylcarbamate.

Schweikl et al. (1996) reported no difference in mutagenicity in TA102 from extracts of a glutaraldehyde-containing dental preparation material using saline or DMSO. Significantly, deKok et al. (1992) reported that neither DMSO nor TBA had any effect on the mutagenicity of fecapentaene-12 in TA102, while superoxide spin trappers greatly reduced mutagenic response. The authors asserted that both DMSO and TBA are hydroxyl radical scavengers. If TBA is an oxygen scavenger, it cannot also be an oxygen generator.

The CARB Report correctly reports that TBAc when dissolved in DMSO is negative for mutagenicity in the standard *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100, as well as in TA102. The report states that "The use of DMSO as a carrier solvent in the study by Huntingdon Life Sciences Ltd. (2000c) is sufficiently confounding that the results of

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[2] CARB notes that the negative TA102 assay of TBAC also used DMSO as a solvent.

this study should be considered inconclusive." Considering this report as inconclusive is important to the CARB position because the report cites a positive study of tertiary butyl alcohol (TBA) in TA102 when dissolved in water (Williams-Hill, 1999) as the primary evidence that TBA is mutagenic and therefore, TBAc should be regarded as mutagenic.

This conclusion is unfounded. In the first place, TBAc cannot be tested without a solvent such as DMSO as it is practically insoluble in water. It most certainly would be negative in strain TA102 if tested without the presence of DMSO because essentially no TBAc would be present. Secondly, Dillon et al., 1992 found little evidence in support of the hypothesis that there are substances that can be detected as mutagens with *S. typhimurium* TA102 that cannot be detected using TA100; strain TA102 is not uniquely sensitive to either reactive oxygen species or aldehydes, since strain TA100 also reacts with these chemical species (Dillon et al., 1998). Thirdly, the scavenging property of DMSO is not an important factor in reducing sensitivity to either reactive oxygen species or aldehydes (Dillon et al., 1998; Fiala et al., 1987). In addition, TBA is regarded as an oxygen radical scavenger, not a generator of oxidative damage. TBA is reported to inhibit prostaglandin synthesis by scavenging needed hydroxyl radicals (Panganamala et al., 1976) as well as to protect DNA from the effects of radiation (LaFleur and Loman, 1982; Reuvers et al., 1973; Roots and Okada, 1972).

In further opposition to the draft report speculation, attempts to repeat the Williams-Hill results in a GLP-compliant laboratory were not successful (McGregor et al., 2005). TBA was not mutagenic in TA102, with or without metabolic activation, when dissolved in water (1 lab) or dissolved in DMSO (2 labs). In the studies reported by McGregor et al. (2005), no toxicity or increased mutations were found at levels up to 5000 µg/plate, whereas Williams-Hill et al. (1999) reported toxicity from TBA at levels above 2000 µg/plate. 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.

With the exception of the questionable result in 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 sum, Lyondell has found no evidence in the literature that DMSO should not be used in Ames assays using TA102 or that DMSO would interfere with the mutagenicity assay of TBA (or that of TBAC). Furthermore, TBA did not have any effect on the mutagenicity of another chemical assayed in TA102. Thus, the weight of evidence – numerous negative tests[3] against one equivocal test that was not reproducible – strongly indicates that TBA is not genotoxic.

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[3] *In vitro* tests include Salmonella and mouse lymphoma cell mutations tests, and Chinese hamster ovary cell sister chromatid exchange and chromosomal aberration tests, all done with and without metabolic activation. *In vivo* tests include frequency of micronucleated erythrocytes in mice and induction of micronucleated erythrocytes in rat bone marrow cells.

B. The Evidence for TBA Carcinogenicity in Animals Is Very Limited

Because there are no carcinogenicity studies on tert-butyl acetate (TBAc), the report assessed carcinogenicity based on metabolism of TBAc to TBA. They cited National Toxicology Program (NTP) studies of TBA, for which NTP concluded there was "some evidence of carcinogenicity in male rats" and "some evidence of carcinogenicity in female mice", indicating less than convincing evidence of carcinogenicity.

The CARB report states "At the 24-month termination of the rat bioassay, the incidence of combined adenoma and carcinoma of the renal tubules was found to be significantly increased in the male mid dose group." "No renal tubule adenoma or carcinoma was observed in 227 control male rats in four studies comprising the recent NTP historical control database for drinking water studies indicating the rarity of these neoplasm's in male rats."

Both of these statements are misleading. In male rats, there was no increase in kidney tumors when analyzing the data by the normal pathology procedure of 1 microscopic section per kidney; the incidences of renal tubule cell adenomas or carcinomas were: 1/50, 3/50, 4/50, 3/50 for male rats exposed to 0, 1.25, 2.5, and 5.0 mg/ml in drinking water. Secondly, the statement on the lack of kidney tumors in the control groups of four drinking water studies was also based on the normal pathologic evaluation procedure of 1 slide per kidney, not based on step sectioning.

In the NTP study, in addition to the normal 1 slide per kidney, the investigators also examined 8-9 step sections per kidney and found a significant increase at the mid-dose; the incidences were: 8/50, 13/50, 19/50*, 13/50. No historical control data were presented for kidney tumors in studies with step sectioning. Thus the tumor response in male rats exposed to TBA was extremely weak, if at all and the incidence in control male rats indicates these are not as rare as suggested in the CARB report.

As cited in the report, the International Agency for Research on Cancer (IARC) has established criteria to establish if male rat kidney tumors are related to alpha-2u-globulin. Although not cited in the report, the US EPA has also published criteria for assessing this mode of action (EPA, 1991). The report states "The data indicate that it would not be appropriate to determine that the increased renal tumors observed in TBA-exposed male rats are solely due to a2µ-induced nephropathy. That is because: 1) the dose response relationship between hyaline droplet severity and renal tumor incidence is weak; 2) increased cell proliferation is observed at TBA doses where renal proximal tubule necrosis should not be occurring because hyaline droplet concentrations are not increased; 3) positive TBA genotoxicity data exists; 4) TBA exposure has been demonstrated to cause adverse renal effects (nephropathy, inflammation, transitional epithelial hyperplasia) in female rats. Therefore, the increased renal tumor incidences observed by NTP (1995) in TBA-exposed male rats should be considered to be suitable for use in human cancer risk assessment."

An examination of the mode of action data reveals that 1) It is true that the dose-response relationship for hyaline droplets is weak. However, the dose-response for tumor data is also very weak (1, 3, 4, 3 tumors/group based on single slide evaluation and 8, 13, 19, 13 tumors/group based on step sections). It would be unusual to find a strong dose-response for hyaline droplet

formation with an extremely weak tumor response. 2) Increased cell proliferation was seen at lower doses than hyaline droplets. Cell proliferation may be a more sensitive method of assessing cellular response than accumulation of protein droplets. 3) As stated above, the genotoxicity data for TBA are overwhelmingly negative. The one positive study cited in the report was not reproducible by independent testing. 4) The report seems not to understand kidney pathology in older rats. As rats age a chronic pathology occurs to varying degrees in the kidney; this is referred to as Chronic Progressive Nephropathy (CPN). Advanced stages of CPN result in inflammation and hyperplasia of the transitional epithelia. It needs to be pointed out that α2u-related hyperplasia occurs only in **tubules** of male rats, but CPN occurs in both males and female. In general CPN is more severe in males than in females. The hyperplasia reported in females exposed to TBA occurred in the transitional epithelia of the **renal pelvic lining**, not in the tubules. 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.

As reported in the NTP study, exposure to TBA caused an exacerbation of CPN to advanced stages and was contributor to mortality in TBA-treated animals. Advanced CPN may also be a contributor to kidney tumors in rats. CPN is a rat specific disease and does not occur in humans. Thus although one cannot say definitely that all the tumors in male rats exposed to TBA were caused by α2u-related toxicity because CPN also played a role, one can conclude that the tumors seen occur by modes of action that do not occur in humans. Thus the marginal increase in kidney tumors in TBA exposed male rats is NOT relevant for human risk assessment.

The report further cites a slight increase in thyroid adenomas in female mice exposed to TBA (judged by NTP to provide "some evidence of carcinogenicity in female mice") as evidence for considering TBAc a human carcinogen. The incidences were 2/58, 3/60, 2/59, and 9/59* for female mice exposed to 0, 5, 10, and 20 mg TBA/ml drinking water. The daily doses were calculated as 0, 510, 1020, and 2110 mg/kg/day, respectively.

Increased thyroid tumors from TBA in mice at such a high dose (only at 20 mg/ml or 2110 mg/kg/day) may not be relevant for TBAc. Using standard conversion factors of mouse body weight at 30 grams and minute volume of 0.023 liters (Melley and Akman, 1994) and a 50% conversion of TBAc to TBA (as indicated in industry-sponsored studies submitted previously to CA EPA), 2110 mg/kg/day TBA translates in to a six-hour TBAc exposure of 15,200 mg/m^3, or 3000 ppm. Preliminary results from a two-week inhalation study of TBAc in mice indicates mice cannot tolerate 3000 ppm TBAc. Thus it is not possible to expose mice to the level of TBAc that could produce increased thyroid tumors.

In conclusion, the slight increase in renal tumors in male rats exposed to TBA appears to be related to α2u, 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. Furthermore, a weak increase in thyroid tumors in mice exposed to a very high dose of TBA that could not be achieved by exposure to TBAc should not be used to infer TBAc carcinogenicity. TBAc has been negative in a battery of genotoxicity tests and should not be

presumed to be carcinogenic based on theoretical considerations in the absence of data. Further, potency calculations should not be performed on such speculation.

Section 3.2.5 of the draft CARB assessment briefly summarizes the NTP 2-year cancer bioassay on TBA that is the basis for the concern that TBA (and, therefore TBAC) might pose a potential cancer risk to humans (NTP, 1995). However, the draft assessment does not provide a weight-of-the-evidence evaluation for that study. It also makes some statements that are inaccurate or misleading.

In Section I.C, below, we discuss the relevance for human risk assessment of the tumors seen in rats and mice, if those observations are considered to demonstrate carcinogenic activity in rodents. As a preliminary matter, in this section, we explain that even the evidence for carcinogenicity in rodents is very limited.

1. Weight of Evidence

The NTP did provide a strength-of-evidence evaluation for the results of its study of TBA. NTP rates the results of its studies as showing "clear," "some", "equivocal" or "no" evidence of carcinogenicity.[4] NTP rated the data on TBA as follows:

Male rats: some evidence (increased kidney tumors)

Female rats: no evidence

Male mice: equivocal evidence (marginal increase in thyroid follicular cell tumors)

Female mice: some evidence (increased thyroid follicular cell tumors)

NTP did not consider any of the tumor data to present "clear" evidence of carcinogenicity. A closer look at the data from the NTP study reveals that even a finding of "some evidence" of carcinogenicity is tenuous.

2. Kidney Tumors

With respect to kidney tumors, NTP initially applied a standard protocol for histopathology, taking one section per kidney. The tumor incidence in the male rats was 1/50, 3/50, 4/50 and 3/50 at the control, low-dose, mid-dose, and high-dose, respectively. Under this protocol, there were no statistically significant increases in male rat renal tubule tumors.

After the results for the original protocol were tabulated, there was a change in the protocol for male kidneys only. An additional 6 to 8 step sections per male kidney were taken from the residual wet kidney tissue. The resulting tumor incidence then became 8/50, 13/50, 19/50, and 13/50, which is statistically significant at the mid-dose, but not at the low- or high-

[4] "About These Long-Term Studies," National Toxicology Program, http://ntp-server.niehs.nih.gov/htdocs/LT-studies/about-abstracts.html (last revised, July 9, 2001).

dose. This change in protocol was controversial, as indicated in the comments of the reviewers reported in NTP (1995). Dr. Ward of NCI noted that, for the standard protocol, there was no statistically significant increase in tumors, so that "no evidence" would be the appropriate classification. For the extended evaluation, based on the statistical increase for only one dose group, Dr. Ward believed "equivocal evidence" would be the appropriate classification.

Furthermore, as explained in Lyondell's August 2001 submission, it is the opinion of Dr. Gordon Hard, a foremost expert on rodent kidney toxicology,[5] that the tumors seen in the step sections probably were due to advanced chronic progressive nephropathy (CPN), a common condition in aged rats that is not relevant to humans. The CPN may have been exacerbated by TBA, but the tumors would not have been due to carcinogenic action of TBA.

No increase in kidney tumors was observed in the female rats. The draft CARB assessment states: "Although no renal tumors were observed in female rats, the incidence of renal hyperplasia was significantly elevated in the high dose group." (p. 21) This statement is misleading. Although increased incidence of transitional epithelium hyperplasia was seen in the kidneys of high dose female rats exposed to TBA, that effect is unrelated to formation of kidney tumors.[6] Only one rat in this group was observed to have renal tubule hyperplasia, the precursor of adenoma. Such a single occurrence does not support the existence of a background of atypical hyperplasia that is expected with an induced carcinogenic effect, and has to be regarded as incidental.

The draft CARB assessment also states: "No renal tubule adenoma or carcinoma was observed in 227 control male rats in the four studies comprising the recent NTP historical data base for drinking water studies indicating the rarity of these neoplasms in male rats." This does not provide a true perspective of spontaneous renal tumor incidence in the male Fischer 344 rat. For example, the NTP records a historical control range of 0-6% (mean 0.98%) renal adenomas and carcinomas combined for untreated male F344 rats, based on single sections from 1,627 animals, and a range of 0-16% (mean 4.62%) for control F344 males after step-sectioning the kidneys of 649 animals (Eustis et al, 1994). The TBA study was conducted within the timeframe for these historical controls. The draft assessment does not provide a time period for the "four recent studies", but it seems likely that these were done after the TBA study.

3. Thyroid Follicular Cell Tumors

With respect to thyroid follicular cell tumors, the only statistically significant increase was at the high dose in female mice. (Tumor frequency was 2/58, 3/60, 2/59 and 9/59 for the control, low-dose, mid-dose and high-dose, respectively.) The tumors were all adenomas (benign tumors); there were no carcinomas (malignant tumors). The frequency of tumors in the control and lower doses is essentially equal with that of the control, indicating the tumor response at the high dose may represent a threshold event.

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[5] See note 3, below.

[6] As stated in Dr. Hard's opinion, the NTP noted that that there was no progression of transitional epithelial hyperplasia to benign or malignant neoplasms (Hard, 2001, p. 5).

4. Summary

As discussed below, the evidence indicates that the male rat kidney tumors are due to a mechanism not relevant to humans and that the follicular cell tumors in female mice may be due to a threshold mechanism. Even apart from those considerations, however, the evidence for carcinogenicity in rodents is quite limited. In rats, only one type of tumor was increased in males only, at the mid-dose only, and only by applying a non-standard protocol. In mice, only one type of tumor was observed, statistically increased in females only, and at the high dose only.

Lyondell requests that final CARB assessment explicitly recognize that the animal evidence for carcinogenicity is limited. In particular, the assessment should note that NTP did not find the results of its study to provide "clear evidence" of carcinogenicity, that there was no evidence for increased male rat kidney tumors based on results from the standard protocol, and that the increase in tumors in the extended protocol may have been due to exacerbation of CPN rather than carcinogenic action of TBA and thus not relevant for humans. The final assessment also should include corrected information on female renal tubule hyperplasia and historical control data for renal tumors in male rats, as described above.

C. There Is Strong Evidence that the Male Rat Kidney Tumors Are Due to a Mechanism Not Relevant to Humans

Lyondell's August 2001 submittal explained how the data for TBA meet each element of both the U.S. Environmental Protection Agency (USEPA) and International Agency for Research on Cancer (IARC) criteria for the alpha-2u-globulin mechanism for male rat kidney tumors. Those criteria were developed by USEPA and IARC to indicate when male rat kidney tumors should be disregarded for purposes of human risk assessment. The draft CARB assessment nevertheless concluded that the male rat kidney tumors should be used for its risk assessment. In doing so, the draft assessment failed to report the conclusions of leading experts and researchers that the USEPA and IARC criteria are met. The draft assessment also presented several arguments against the applicability of the alpha-2u-globulin mechanism; for the reasons given below, Lyondell believes those argument provide insufficient reason to reject the experts' conclusion that the male rat kidney tumors are not relevant for human risk assessment.

1. Independent Experts Have Concluded that the Male rat Kidney Tumors Are Not Relevant to Human Risk Assessment

Lyondell's August 2001 submittal included an opinion by Dr. Gordon C. Hard, a leading expert in rodent kidney toxicology and the alpha-2u-globulin mode of action for male rat kidney tumors.[7] Dr. Hard's opinion was that the male rat kidney tumors seen in the NTP study

[7] As stated in Lyondell's August 2001 submittal, Dr. Hard was instrumental in developing research on the alpha-2u-globulin (α_{2u}-g) mode of action. He was a principal author of USEPA's Risk Assessment Forum "purple book" on α_{2u}-g that developed criteria for determining when renal tumors in male rats should be disregarded for human risk assessment (USEPA, 1991). Dr. Hard also was a member of a 1997 *ad hoc* Expert Working Group of IARC, which provided the initial foundation for IARC's scientific paper on the α_{2u}-g mechanism (Swenberg and Lehman-

meet the criteria for being due to the alpha-2u-globulin mechanism, and therefore are not relevant to humans (Hard, 2001). The Lyondell submittal also included a paper by Williams and Borghoff (2001), who concluded that each element of both the USEPA and IARC criteria for an alpha-2u-globulin mechanism have been met for TBA.

Curiously, although the draft CARB assessment refers to the expert opinion of Dr. McClain, which was submitted in Lyondell's August 2001 package with respect to the thyroid follicular cell tumors, the draft assessment includes no mention of Dr. Hard's opinion. Nor does the draft assessment mention the Williams and Borghoff (2001) paper. The draft assessment does cite two papers which it characterizes as raising "the possibility" that the male rat tumors "may be related to a TBA-α2μ" mechanism" (Borghoff et al., 2001; McGregor and Hard, 2001). Lyondell believes this characterization understates the conclusions of those papers. More significantly, however, those papers were published before a final piece of data had been developed with respect to the criteria. The Williams and Borghoff (2001) paper provided that final piece of data, which led the authors to then definitely conclude that each element of both the USEPA and IARC criteria for an alpha-2u-globulin mechanism have been met for TBA (Williams and Borghoff, 2001). Those data also were cited by Dr. Hard in his opinion that the criteria for an alpha-2u-globulin mechanism are met by the TBA data.

The significance of the alpha-2u-globulin mechanism is that it is a mechanism which operates in male rats, but not in humans. The USEPA and IARC criteria were developed to enable risk assessors to know when male rat kidney tumors should be disregarded for purposes of human cancer risk assessment. In the opinion of Dr. Hard and of Williams and Borghoff (2001), the USEPA and IARC criteria have been met, indicating that the kidney tumors observed in the TBA bioassay should be disregarded.

As explained in Dr. Hard's opinion, and discussed above (Section I.B.2), an alternate or additional mechanism for the male rat kidney tumors is exacerbation of chronic progressive nephropathy (CPN), a spontaneous background lesion in rats. In Dr. Hard's opinion, whether the tumors were due to alpha-2u-globulin, enhanced CPN, or both, the mechanism leading to the tumor formation has no relevance for human risk assessment.

Lyondell requests that the final CARB assessment recognize the expert opinions of Dr. Hard (Hard, 2001) and of Williams and Borghoff (2001), indicating that the male rat kidney tumors should be disregarded for purposes of human risk assessment of TBA (and, thus, TBAC).

2. The Data Are Sufficient to Conclude that the Male Rat Kidney Tumors Should Not Be Used for Human Cancer Risk Assessment

The draft CARB assessment (p. 22) lists four arguments that "it would not be appropriate to determine that the increased renal tumors observed in TBA-exposed male rats are

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McKeeman, 1999). He further was a member of the 1998 Expert Working Group for IARC monographs that re-evaluated the carcinogenicity classification of *d*-limonene in light of the α_{2u}-g nephropathy evidence (IARC, 1999). A copy of Dr. Hard's *Curriculum vitae* was provided in the August 2001 submittal.

solely due to α2μ-induced nephropathy." For the following reasons, Lyondell believes those arguments are not sufficient to overcome the conclusion that the TBA data tumors meet the USEPA and IARC criteria for the alpha-2u-globulin mechanism.

The first two arguments given by the draft assessment are: "1) the dose response relationship between hyaline droplet severity and renal tumor incidence is weak; 2) increased cell proliferation is observed at TBA doses where renal proximal tubule necrosis should not be occurring because hyaline droplet concentrations are not increased." However, it is important to understand that the cell proliferation, hyaline droplet accumulation, and renal tumor induction data were developed through several studies. The less than perfect correlation among these parameters is typical when data extrapolations are made between studies or different techniques are used within the same study for demonstrating different effects (Hard, 2002). In addition, it must be noted that TBA is only a weak alpha-2u-globulin inducer and that the increases in renal tumors were slight; therefore, dose-response relationships can easily be obscured by random noise in the studies.

The over-riding point is that hyaline droplet accumulation and increased cell proliferation are present, and both involve the tubules of the cortex. The less than perfect correlations noted in the draft assessment are a relatively minor aspect that should not be used to discredit the otherwise robust association that has been described, that is, the convincing and predictive histological features and biochemical data (Hard, 2002).

In this latter respect, the draft assessment fails to accord the various histopathological changes appropriate weight (Hard, 2002). The hyaline droplets observed in renal cortical tubules of male rats treated with TBA have been demonstrated to represent alpha-2u-globulin, including large angular, crystalline structures indicative of an injurious level of cellular accumulation. Furthermore, the presence of a clearly dose-related increase in linear papillary mineralization, regarded as pathognomonic of alpha-2u-globulin nephropathy, implies that the cell injury from the protein accumulation was continuous and sufficient to produce sustained downstream effects in the papilla. Not all compounds binding to alpha-2u-globulin, and thus leading to hyaline droplet accumulation, result in long-term renal tumor formation, and these examples tend *not* to be associated with linear papillary mineralization, implying that they have not caused a necessary threshold of sustained tubule damage (Williams et al., 2001).

The third point provided in the draft assessment to dispute applicability of the alpha-2u-globulin mechanism theory is that "3) positive genotoxicity data exists." However, as discussed in Section I.A, that data consists of a single *Salmonella*/mammalian mutation assay in TA102 that, at best, was only marginally positive and that was not replicable in a second TA102 assay. The draft assessment posits that the repeat assay was negative because of the DMSO solvent used, but, as discussed above, the literature does not support that supposition. This single, non-replicable, marginally-positive test stands in contrast to a large number of other *in vitro* and *in vivo* negative tests. Thus, the weight of the evidence is that TBA is not genotoxic.

Finally, the draft assessment asserts, "4) TBA exposure has been demonstrated to cause adverse renal effects (nephropathy, inflammation, transitional epithelial hyperplasia) in female rats." Lyondell believes it is misleading to say that adverse renal effects exist in the TBA-treated female rats in order to downplay an alpha-2u-globulin related mode of action as

underlying renal tumor induction in the male rats. As discussed in Dr. Hard's opinion (Hard, 2001), the "nephropathy" cited here is of spontaneous origin, representing a rodent-specific entity (chronic progressive nephropathy, CPN) with no counterpart in humans (see also USEPA, 1991). TBA appears to have exacerbated the CPN, a common finding with many chemicals of diverse structure, but this is not a nephrotoxic effect. In the NTP study, the female rats from treated groups were not described as having renal changes indicative of cytotoxicity. The inflammation was bladder-related, and not of renal origin. The transitional epithelial hyperplasia would certainly have been linked with the exacerbated CPN and/or the tendency for calculus formation, rather than being a manifestation of TBA-induced nephrotoxicity (Hard, 2001; Hard 2002).

Thus, we believe the reasons set forth in the draft assessment are insufficient to deny that the criteria for an alpha-2u-globulin mechanism have been met. A balanced consideration of the data shows that there are strong data that clearly support an alpha-2u-globulin basis for the renal tubule tumor induction by TBA in male rats only (Hard, 2002).

D. The Available Data Support the Hypothesis that the Thyroid Follicular Cell Tumors in Mice Are Due to a Threshold Mechanism

As acknowledged by the draft CARB assessment, the Lyondell August 2001 submittal included an opinion by Dr. Michael McClain, a leading researcher in the mode of action for thyroid tumors.[8] Dr. McClain concluded:

> The findings of thyroid follicular cell hyperplasia in male and female B6C3F1 mice and an increase in the incidence of follicular cell adenoma in female mice in a 2-year carcinogenicity study are compatible with a proliferative response secondary to hormone imbalance. The most likely hypothesis is altered thyroid hormone disposition as a result of microsomal enzyme induction in TBA treated mice. There is no evidence for a mutagenic or clastogenic effect of TBA, thus a genotoxic mode of action is very unlikely (McClain, 2001).

That is, the data for the thyroid tumors in mice treated with TBA are consistent with a threshold mechanism for the tumor formation.

The draft CARB assessment points out that Dr. McClain did not state that the female mouse thyroid tumor data were inapplicable to human cancer risk assessment. This is misleading, since the actual question for such tumors is whether they should be treated as a threshold phenomenon for human risk assessment. As acknowledged in Lyondell's August 2001

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[8] As stated in Lyondell's August 2001 submittal, Dr. McClain was an independent peer reviewer for USEPA's Risk Assessment Forum report, Assessment of Thyroid Follicular Cell Tumors, and was a member of the 1997 IARC working group for mechanisms of carcinogenesis that may be species specific. He currently is Chairman of the Thyroid Subgroup of the Carcinogenicity Working Group, International Life Science Institute (ILSI) Risk Science Institute. A copy of Dr. McClain's curriculum vitae was provided with the August 2001 submittal.

submittal, not all studies have been conducted to demonstrate that the USEPA criteria for using a threshold model have been met. However, Dr. McClain's opinion shows that some of the criteria have been met, and that the available data are compatible with a threshold mechanism for TBA carcinogenicity in the mouse. Lyondell believes that it is important that this point be acknowledged, to put the mouse thyroid data in proper perspective.

The draft CARB assessment sets forth four arguments against a threshold mechanism for the thyroid tumors. One is that "positive genotoxicity data for TBA have been published." As discussed in Sections I.A. and I.C.1, that data consists of a single *Salmonella*/mammalian mutation assay in TA102 that was equivocal and non-replicable. Although the draft assessment posits that the repeat assay was negative because of the DMSO solvent used, the literature does not support that supposition. Against this single, non-replicable, equivocal test stands a large number of negative *in vitro* and *in vivo* tests. Thus, the weight of the evidence is that TBA is not genotoxic. The opinions of Both Dr. Hard and Dr. McClain agree that TBA is unlikely to act through a genotoxic mode.

A second argument the draft assessment gives against a threshold mechanism is "There is no TBA cytochrome P450 induction data available for mice. The indirectly supporting evidence for cytochrome P450 induction in rats is weak." However, as discussed in Dr. McClain's opinion, there is evidence for microsomal enzyme induction of TBA in both rats and mice. For rats, Bechtel and Cornish (1972) studied the microsomal enzyme inducing capabilities of several alcohols including TBA via oral and intraperitineal administration. They found a threefold elevation of the microsomal enzymes, acetanilide dehydrogenase and aminopyrine demethylase. Aarstad et al. (1985) studied changes in the cytochrome P450 enzyme systems following the inhalation of several butanols. SD rats were exposed to the different butanol isomers, including TBA, for three days at 2000 ppm and five days at 500 ppm. Three days of exposure to TBA at 2000 ppm induced hepatic cytochrome P450 and increased the metabolism of n-hexane.

For mice, McComb and Goldstein (1979) noted an increase in the rate of elimination of TBA from the bloodstream of mice previously exposed to TBA. The increased elimination of TBA was considered to reflect an induction of the smooth endoplasmic reticulum, which is also known to occur after exposure to ethanol.

In addition to the above studies, the relative liver weights were increased in both rats and mice in the sub-chronic toxicity studies, which is also consistent with microsomal enzyme induction. Thus, there is evidence that TBA is a microsomal enzyme inducer in both rats and mice. There is also information for some other chemicals that are metabolized to TBA and thought to act via TBA demonstrating the induction of microsomal enzymes. Although the number of studies is not large, the evidence is not "weak" (McClain, 2002).

A third argument in the draft CARB assessment against a threshold mechanism is that "NTP (1995) noted that no evidence of thyroid follicular cell hyperplasia was observed in mice exposed orally to TBA for 13 weeks." However, Dr. McClain reports:

> In my experience with weakly goitrogenic chemicals, follicular cell hypertrophy and hyperplasia are often overlooked in

> subchronic studies. This is because the changes are subtle and there is a great deal of variation in the morphology of the rodent thyroid gland. It is not uncommon after the observation of thyroid tumors at the end of the two-year study, for a re-evaluation of thyroid glands from the short-term studies by an experience pathologist, to reveal follicular cell hypertrophy. With weakly goitrogenic chemicals, follicular cell hyperplasia is less often observed in sub-chronic studies than hypertrophy. (McClain, 2002)

A fourth argument advanced by the draft CARB assessment is that "No data exists indicating that TBA results in increased thyroid stimulating hormone (TSH) or decreased thyroxine (T4) levels in either rats or mice." This is true, and is a reason neither Dr. McClain nor Lyondell has asserted that there is proof that the thyroid tumors are due to a threshold mechanism. However, in view of the information that is available in the published literature on the weight of evidence for genotoxicity, overall toxicity, and the other biological effects of TBA, it appears unlikely that TBA is a genotoxic carcinogen (McClain, 2002).

Thus, while the current state of the data does not allow for an incontrovertible finding that the thyroid tumors in female mice should be assessed using a threshold model, the available data do strongly point in that direction. To provide a balanced perspective of the data, the final assessment should acknowledge that the existing data are consistent with a threshold mechanism for the thyroid follicular cell tumors.

II. THE RISK ASSESSMENT USES CONSERVATIVE ASSUMPTIONS AT EVERY STEP IN THE ANALYSIS AND THEREFORE GREATLY OVERSTIMATES THE POTENTIAL HUMAN HEALTH EFFECTS FROM USE OF TBAC

The draft CARB assessment provides an estimate of potential human chronic health consequences if the VOC exemption is granted and TBAC replaces existing solvent uses in California. This estimate uses 1) assumptions about solvent use replacement volumes, 2) a calculated cancer potency for TBAC (expressed as an inhalation unit risk value) and 3) modeling of TBAC air concentrations. The draft assessment also includes a brief evaluation of potential acute human health effects, which relies on an estimated acute reference exposure level (REL).

For each of these elements of the risk assessment, the draft assessment uses “worst-case” assumptions which, taken individually appear reasonable to protect human health, but whose cumulative effect is to greatly overestimate the potential human health effects.

Lyondell believes CARB should revise its risk assessment in accordance with the information presented below. At the least, the final assessment should acknowledge that the cumulative effect of its conservative assumptions may be to greatly overestimate the actual health risks from TBAC usage. The report or the response to these comments should also explicitly state that it is possible the human health risks from use of TBAC are much lower than those estimated using those multiple conservative assumptions.

A. The Quantitative Cancer Risk Assessment for TBAC Is Overly Conservative

Because the draft CARB assessment found the animal carcinogenicity data for TBA relevant for human risk assessment, the assessment (p.23) used an oral cancer slope factor (CSF) derived for TBA to calculate an inhalation unit risk value for TBAC of 4×10^{-7} $(\mu g/m^3)^{-1}$. For several reasons, this value is excessively conservative. There is a strong possibility that TBAC poses no carcinogenic risk to humans. Even if it TBAC does pose a non-zero risk, the assumptions used to derive the unit risk value in the draft assessment are excessively conservative.

1. Available Evidence Indicates that a Carcinogenicity Assay of TBAC Would Be Negative

There is no direct evidence that TBAC is a carcinogen. Rather, there is limited evidence that a metabolite of TBAC – TBA – may be an animal carcinogen. In its August 2001 submission (pp. 15-16), Lyondell explained that, based on the metabolism and toxicity of TBAC in rats and mice, it is likely that neither rats nor mice would survive sufficient concentrations of TBAC to generate blood levels of TBA sufficient to induce either kidney tumors in male rats or thyroid tumors in female mice. Increased kidney tumors from TBA exposure were seen in male rats exposed to 200 and 420 mg/kg/day, but not at 90 mg/kg/day (using data from step sectioning). Rats would have to be exposed to 2500 ppm TBAC for two years to achieve 200 mg/kg/day TBA in a cancer bioassay. Because liver toxicity was seen at 1643 ppm for two weeks, it is unlikely rats would survive for two years at 2500 ppm. Further, mice would have to be exposed to 25,000 ppm for two years to achieve the level of TBA that induced thyroid tumors in female mice. This concentration is 5-6 fold higher than the acute LC_{50} in rats and clearly is higher than the expected LC_{50} in mice.

Thus it is unlikely that either rats or mice would survive exposure to concentrations of TBAC that would produce enough TBA to cause tumors. This suggests that a bioassay of TBAC would be negative, providing no support for a finding of human cancer risk from exposure to TBAC.

2. Available Evidence Indicates that the Human Cancer Risk from TBAC Exposure May Be Zero

The unit risk value for TBAC is calculated on the assumption that the incidence of tumors in rats and mice exposed to TBA is relevant for human exposures to TBA through metabolism of TBAC. However, as discussed in Section I.B, even the evidence for animal tumors from TBA exposure is quite limited. Although no agency has assigned a cancer classification to TBA, Lyondell believes that no agency would find the existing data to support a classification of "probable human carcinogen" for TBA.

As discussed in Section I.C, the data support a finding that the male rat kidney tumors are not relevant for human risk assessment. The data further indicate it is likely the female mouse thyroid tumors were due to a threshold mechanism (Section I.D). Since the TBA dose at which the female mouse thyroid tumors occurred was 2110 mg/kg/day, and yet higher

doses of TBAC would be required to achieve such TBA levels, there is very little likelihood that humans would experience exposures sufficient to cause such tumors.

Thus, there is a strong possibility that the true human cancer risk from either TBA or TBAC exposure is zero. On the basis of the available evidence, Lyondell believes that any human health estimate for TBAC should be based on a nonthreshold endpoint. If the final assessment nevertheless includes a cancer risk estimate, it should also acknowledge that the true cancer risk might be zero.

3. It Is Inappropriate to Base the Cancer Slope Factor on the Male Rat Kidney Tumors

The draft CARB assessment (p. 23) uses an oral cancer slope factor (CSF) for TBA calculated by OEHHA. OEHHA calculated that CSF from the incidence of kidneys tumors in males (OEHHA, 1999). Lyondell believes that it is inappropriate and therefore excessively conservative to use the male rat kidney tumors as the basis for a CSF for the reasons described in Sections I.B.2 and I.C. As explained there:

- There was no increase in male rat kidney tumors under the standard protocol.

- Under the extended protocol (extra step sections of kidney tissue), tumors were significantly increased only at the mid-dose. In the opinion of Dr. Hard, the tumors seen with the step sectioning probably were due to advanced chronic progressive nephropathy (CPN), a common condition in aged rats that is not relevant to humans, rather than being due to carcinogenic action of TBA.

- In the opinion of Dr. Hard and of Williams and Borghoff (2001), and as detailed in Lyondell's August 2001 submittal, the TBA data meet both the USEPA and IARC criteria for when kidney tumors are due to an alpha-2u-globulin mechanism and therefore are not relevant for human risk assessment.

For these reasons, if any CSF is calculated for TBA, it should be based on the female mouse thyroid tumor data rather than the male rat kidney tumor data. Using OEHHA's methodology, the thyroid tumor data would give a CSF for TBA of approximately 0.0005 $(mg/kg\text{-}day)^{-1}$ -- a value that is 6-fold less than the value used for the draft CARB assessment.

We note that even calculating a CSF based on the thyroid tumor data is conservative, since it is likely that those tumors were due to a threshold mechanism, whereas the CSF assumes a non-threshold linear response. Furthermore, the CSF methodology itself uses a number of conservative assumptions, such as using the upper bound value (versus the best estimate).

4. It Is Inappropriate to Assume 100 Percent Conversion of TBAC to TBA

To convert the cancer slope factor for TBA to a cancer slope factor for TBAC, the draft CARB assessment "conservatively assumed that at the lower environmental exposure levels expected to result from TBAC commercial use, 100 percent of inhaled TBAC would be

metabolized to TBA." (p. 23) The rationale provided for this assumption is that "Relatively high-dose (100 ppm) exposures to TBAC by inhalation in rats (HLS, 2000b) indicated that greater than 95 percent of the inhaled TBAC dose was excreted in urine or feces or retained in tissues as metabolites." However, not all of those metabolites were TBA.

The Huntingdon study (HLS, 2000b) indicates that, at 100 ppm TBAC, no more than 45% of metabolism is to TBA, while 45% is metabolized through 2-hydroxymethylisopropyl acetate. The major urinary metabolite is 2-hydroxyisobutyric acid, which could come from 2-hydroxyisopropyl acetate or TBA; thus it is possible that even more than 45% of TBAC is metabolized by hydroxylation rather than by hydrolysis to TBA. Further, the Huntington study data indicate that the hydroxylation pathway is favored at lower concentration, and that, as this pathway becomes saturated, hydrolysis becomes more important.[9]

Thus, 45% hydrolysis to TBA should represent a maximum for the low exposures that would occur from TBAC commercial use. If a CSF is derived for TBAC from the TBA data, it should assume 45% conversion to TBA, not 100%.

5. CARB Should Reevaluate the Cancer Risk Assessment for TBAC

For the reasons described above, Lyondell disagrees with calculation of a human cancer risk value for TBAC using a nonthreshold linear extrapolation model. Rather, we believe the data indicate that use of a threshold endpoint is appropriate.

If CARB nevertheless calculates a linear-extrapolation cancer slope factor for TBAC, it should be based on the TBA female mouse thyroid tumor data rather than the male rat kidney tumor data. Furthermore, derivation of the TBAC CSF from the TBA CSF should be based on an assumption of no more than 45% conversion of TBAC to TBA.

Lyondell calculates that the resulting inhalation unit risk value would be approximately 2.9×10^{-8}, a value 14-fold below the value used for the draft assessment. Lyondell believes that even this value greatly overstates the potential cancer risk to humans, since it is unlikely that TBAC is a nonthreshold carcinogen, or even that it is a carcinogen at all.

B. The Draft Assessment Likely Overstates TBAC Usage Volumes

Lyondell agrees with the draft CARB assessment's list of the top five solvents that TBAC is likely to replace (toluene, MEK and three xylenes). However, the volume projections for replacement of these solvents are substantially higher than we believe is likely for the California market. Specifically, we do not believe that TBAC will see much use as a replacement for compliant formulations. Such formulations meet the current VOC limits and, therefore, there is little incentive to reformulate. One exception could be instances to replace PCBTF, where TBAC could provide compliance at a lower cost.

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[9] Inhalation of 1000 ppm TBAC for six hours resulted in a shift toward hydrolysis (67%) with a reduction in hydroxylation (27%).

The report lists Texanol and vinyl acetate as two solvents likely to be replaced, at least in part, with TBAC. This is highly unlikely. Texanol is a coalescent for water-based latex paint. The volatility of TBAC is greater than water and it cannot be used as a coalescent. Also, vinyl acetate is a monomer for vinyl resins and is not used as a solvent in coating formulations.

Lyondell also is surprised that automotive care products -- in particular, brake cleaners -- are viewed in the draft assessment as such a large replacement opportunity for TBAC. We have had some feedback from that market which indicates that TBAC does not have sufficient solvency for the types of soils encountered in brakes. In addition, comments have indicated that its odor may make TBAC unacceptable for this application. Given the differences in physical properties between TBAC and perc, it seems unlikely that a 100% replacement would be feasible.

Therefore, Lyondell believes that the total volume of TBAC used in California is likely to be less than that used for the draft assessment. This in turn would mean air concentrations would be less, and so the potential human health effects would be less.

C. The Air Quality Modeling Methodology Uses Some Excessively Conservative Assumptions

Lyondell requested that ENSR review the air quality modeling for the draft CARB assessment. A copy of the ENSR report is provided as Appendix A. As discussed therein, the methodology used in the draft CARB assessment is generally reasonable. However, in several instances, the assumptions chosen are very conservative, leading to an overestimation of the cancer risk. Two factors, in particular, greatly influence the risk estimate. First, the estimates of risk were based on estimated outdoor TBAC concentrations, without adjustment for indoor air concentrations. Consideration of indoor air would reduce the risk by at least 30 percent. Second, the modeling for automotive brake shops and automotive body paint shops assumed persons would be living as close as 30 meters from the facility. However, for the size of the large facilities modeled, such proximity is highly unlikely. A much more appropriate, yet still conservative, distance assumption would be 100 meters. Use of this distance would reduce the risk assessment by approximately 70%.

1. The Risk Assessment Should Account for General Indoor Air Exposures

The draft CARB assessment includes modeling of outdoor concentrations of TBAC in the South Coast Air Quality Management District (SCAQMD), and in the near vicinity of automotive "brake shops" and automotive refinishing facilities. These outdoor air concentrations were then combined with the cancer potency estimate to calculate cancer risks. However, Lloyd and Cackette (2001) report that the average Californian spends upwards of 87% of the time indoors, with a corresponding reduction in potential exposure to toxic air pollutants when compared to a continuous outdoor exposure. CARB recognized this issue in a recent report on reducing cancer risk from diesel particulate matter (CARB, 2000), in which outdoor estimates of diesel particulate concentrations were multiplied by a factor of 0.70 to adjust for lower expected exposure levels indoor. Lyondell believes that a similar factor should be applied to the TBAC assessment.

2. The Estimated Distance of Residences from Facilities Is Overly Conservative

For the brake shop and refinishing facility scenarios, the draft assessment estimates TBAC concentrations at a distance 30 meters from the facility and uses those concentrations to estimate exposures of human living near the facility. Lyondell believes this assumption is unrealistic. For the few large facilities that drive the risk assessment, it is highly unlikely that a residence will be located only 30 meters from the facility. Large commercial automobile repair and refinishing facilities that are the largest potential emitters of TBAC are typically located in commercial areas with little chance of a residence within 30 meters. More likely, the nearest residential areas would be 100 meters or more from these large facilities.[10]

As shown in the ENSR report, concentrations of an air-borne substance drop off rapidly with increasing distance from the source. A value for 100 meters would be only about 30 percent of the value for 30 meters. Consequently, the calculated risk would be lowered by approximately 70 percent.

D. The Cancer Risk for the Brake Shop Scenario Should Be Done on a Comparative Basis

The draft assessment calculates a cancer risk for a "brake shop" scenario, in which it is assumed TBAC will replace use of PERC. The risk of cancer from TBAC exposure is calculated to be less than one to 4 excess cancers per million. However, these values fail to account for the fact that PERC itself is classified as a probable human carcinogen. The inhalation unit risk factor (URF) for perchlorethylene is 5.9×10^{-6} $(\mu g/m^3)^{-1}$ (OEHHA, 2002). This is approximately 15-fold higher than the URF used by the draft assessment for TBAC of 4.0×10^{-7} $(\mu g/m^3)^{-1}$. Thus, the theoretical increase in cancers from TBAC would be more than offset by the theoretical decrease in cancers from perc. Lyondell believes that, if the final assessment continues to treat TBAC as a nonthreshold carcinogen, the assessment calculate the potential cancer risks at brake shops (or any other facility where TBAC would replace perc) on a comparative basis.

E. The Likely Human Cancer Risk Is Far Below that Calculated in the Draft Assessment

The draft assessment calculates potential human cancer risks from use of TBAC to be following for the general population and for persons living near automotive refinishing facilities or "brake shops":

general population	1.1×10^{-6}
automotive refinishing	$<1 \times 10^{-7}$ to 11×10^{-6}

[10] It is possible some residences could be closer than 100 meters to a small facility, but the emissions from such a facility would be much less, so that potential exposures would be far lower.

brake shops $<1 \times 10^{-6}$ to 4×10^{-6}

As the foregoing explains, these values reflect the cumulative use of very conservative assumptions. Lyondell believes any one of the assumptions discussed above is overly conservative; added together, the final risk assessment greatly overstates the likely human cancer risk (which may in fact be zero).

The general population risk estimate of one in a million is right at the value that is usually considered to be an acceptable risk. The lower range values for the automotive scenarios are below that value; the higher ends of the ranges are above it. As discussed in the ENSR report (Appendix A), the typical facility is likely to be closer to the lower value. Thus, even using the very conservative assumptions of the draft assessment, the cancer risk posed by TBAC usage would not be excessive in nearly all scenarios.

However, for the reasons given above, Lyondell believes the final assessment should recalculate the potential health risks using more realistic and appropriate assumptions. We believe it would be most appropriate to not calculate a cancer risk assessment at all. If such an estimate is made, however, the unit risk factor should be based on the female mouse thyroid tumors and should assume no more than 45 percent conversion of TBAC to TBA. This would give a 14-fold reduction in the cancer risk estimate. In addition, a factor of 0.70 should be applied to account for general indoor air exposures. The resulting cancer risk estimate for general population exposures would be:

general population 5.5×10^{-8}

i.e. less than 6 excess cancers in 100 million. This value clearly is well within an acceptable risk.

For automotive refinishing facilities and brake shops, yet a further factor of about 0.3 should be applied for use of a more appropriate distance of 100 meters rather than 30 meters, for large facilities. The resulting high end cancer risk estimates would then be approximately:

automotive refinishing 1.6×10^{-7}

brake shops 6×10^{-8}

Thus, even the highest estimate, based on a large automotive refinishing facility within 100 meters of a residence, gives an acceptable risk estimate (about 2 excess cancers per 10 million).

We note that, to the extent TBAC usage volume is less than assumed in the draft assessment, the estimates would be yet less.

Thus, Lyondell strongly believes that an appropriate cancer risk assessment would indicate that use of TBAC is not likely to present significant cancer risks, if it indeed poses any.

F. An Appropriate Acute REL Would Be Much Higher than 1000 µg/m^3

The draft CARB assessment (p. 43) includes an estimate of maximum one-hour TBAC concentrations for locations near brake shops and automotive refinishing paint booths of 2,800 µg/m^3 and 1,700 µg/m^3, respectively. The draft assessment notes that there is no acute reference exposure level (REL) for TBAC, but that ""OEHHA believes that the available information suggests that an acute REL would likely be about 1000 µg/m^3." The draft assessment further notes that the estimated maximum one-hour concentrations are well below the acute RELs for toluene, xylenes and MEK, substances that TBAC might replace.

Based on the methodology for calculating acute RELs (OEHHA, 1999), it appears that an estimate of an acute REL of 1000 µg/m^3 was derived from the 1958 study at Industrial Biotest Laboratories, which indicated a LOAEL of 500 mg/m^3 for central nervous system effects. However, that 44-year old study was not done according to Good Laboratory Practice (GLP) standards, and its results were not reproducible in two more recent studies that did follow GLP standards (Stillmeadow, 1997; HLS, 1999). Lyondell believes it would be more appropriate to use the LOAEL value from the Huntingdon acute inhalation study, in which mild CNS effects were observed after 6 hours of exposure to 1873 ppm (8878 mg/m^3).[11] This would increase the estimated acute REL to approximately 36,000 µg/m^3.[12] This is very much on a par with the acute RELs for toluene, xylenes, and MEK, which are 37,000 µg/m^3, 22,000 µg/m^3 and 13,000 µg/m^3, respectively.

Lyondell further notes that the acute RELs for toluene, xylenes and MEK are based on no-effect levels from human studies, which exist because of the long-term usage of these chemicals. As a result, the NOAEL value for each chemical is reduced only by a factor of 10 to derive the acute REL. In contrast, the estimated TBAC value is derived from an animal LOAEL. Therefore, an uncertainty factor of 600 is applied to derive the acute REL. Even so, as just shown, an acute REL based on the more appropriate Huntingdon study is in the same range as those for toluene, xylenes, and MEK. It is possible, however, that if adequate human data were available for TBAC, its acute REL would be much higher.

That an appropriate acute REL for TBAC should be in the same range or higher that those for toluene, xylenes, and MEK is supported by the threshold limit values (TLVs) established for these compounds by the American Conference of Governmental Industrial Hygienists (ACGIH). The 8-hour time-weighted TLV values are (ACGIH, 2002):

toluene	50 ppm
xylenes	100 ppm
MEK	200 ppm

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[11] The fact that CNS effects were so mild at this level is further indication that the observation of CNS effects at 500 mg/m^3 in the 1958 Industrial Biotest study is unreliable.

[12] Extrapolated one-hour concentration from 8878 mg/m^3 for 6 hours = 21,747 mg/m^3. Cumulative uncertainty factor = 600 (6 for LOAEL, 10 for intraspecies, 10 for intraspecies).

TBAC 200 ppm

Finally, we note that the higher of the maximum acute exposures (2,800 µg/m^3) was modeled for automotive brake shops, based on the supposition that TBAC would replace PERC usage at those shops. PERC has an acute REL of 20,000 µg/m^3 and a TLV of 25 ppm. Thus, replacement by TBAC would actually represent a ***decrease*** in acute health risks.

G. TBAC Can Be Handled Safely In Commerce

In assessing the potential health effects of TBAC, it is important to keep in mind that TBAC use will not represent a wholly new solvent use where before no chemicals were used. Rather, TBAC will replace use of existing solvents. As is this case with those solvents, Lyondell strongly believes TBAC can be handled safely in commerce. As the foregoing shows, it is highly unlikely that TBAC would pose a human cancer risk. TBAC's toxicity profile compares favorably with that of solvents it would likely replace.

The solvents TBAC most likely would replace are subject to health-related regulations. Toluene is listed as a reproductive toxin under "Proposition 65." Toluene, xylenes, and MEK are all listed as hazardous air pollutants under the Clean Air Act and as Toxic Air Contaminants in California. These regulatory listings underscore the need to handle materials responsibly and safely, but none warrant a ban or imply that the materials cannot be handled responsibly or safely. The same is true for TBAC.

On the other hand, TBAC provides a benefit over these solvents in that it leads to less ozone formation. Ozone is regulated as a criteria air pollutant in part because of its significant adverse human health effects. Thus, use of TBAC will contribute to a reduction in human health effects from ozone.

Control of ozone formation is perhaps one of the most challenging and persistent issues facing California regulators. TBAC works very well as a replacement for other solvents with a net decease in ozone formation. The available evidence strongly indicates that such replacement would not lead to an overall increase in health impacts, and in fact would lead to a decrease in the health impacts of ozone. Lyondell urges that the final CARB assessment not obscure this benefit through the excessive use of conservative assumptions.

III. ADDITIONAL ENVIRONMENTAL IMPACT DATA ARE AVAILABLE FOR TBAC

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." (p. 15) 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.

CONCLUSION

Lyondell requests that CARB quickly exempt TBAC from the definition of a VOC due to its low potential to form ozone and allow its use in all product categories where it is likely to replace more reactive, toxic, or hazardous solvents. Such an exemption would result in the replacement of ozone-forming solvents as well as known, or suspected, human carcinogens such as PERC, TCE, and MC. As recognized in the draft CARB assessment, use of TBAC in California has the potential to provide significant environmental benefits, through reduction in ozone formation and lower TAC exposures. It also will provide economic benefits to formulators who can thus meet stringent VOC regulations.

The draft CARB assessment provides an estimate of potential health impacts of TBAC use, based on the assumption that TBAC is a carcinogen, and applying a number of very conservative assumptions to develop hazard and exposure estimates for TBAC. The weight of the scientific evidence indicates that TBAC use is unlikely to pose a cancer risk, and therefore that no cancer risk should be calculated. If a cancer risk is nevertheless calculated, it should use more appropriate assumptions, as discussed in these comments. The resulting cancer risks would be orders of magnitude below those calculated in the draft assessment and would be well below the generally acceptable risk of one in a million. Furthermore, replacement of even a portion of the PERC, TCE, and MC still used in consumer and industrial products today would likely result in fewer cancer cases even if TBAC itself were to pose a slight cancer risk.

Lyondell therefore believes that CARB should reevaluate its conclusions about the potential human health risk of TBAC usage in accordance with these comments and back away from its current speculation that increased TBAC usage could result in a greater number of cancer cases. This position is simply not supported by the weight of the scientific evidence and could result in more cancer cases and premature deaths from the continued use of more photochemically reactive and carcinogenic solvents. 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.

The final assessment and/or the response to these comments should recognize that TBAC is unlikely to pose significant health risks under realistic use and exposure scenarios. Readers should be provided balanced information to allow a realistic perspective on the weight of any health concerns against the significant environmental and health benefits likely to be provided by increased usage of TBAC.

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APPENDIX A

ENSR INTERNATIONAL REVIEW OF CARB'S DRAFT ENVIRONMENTAL ASSESSMENT OF TBAC

August 1, 2005 *via* e-mail

Dr. Dongmin Luo
Research Division
California Air Resources Board
1001 I Street, 23rd Floor
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dluo@arb.ca.gov

Subject: Staff Report: Environmental Impact Assessment of tertiary-Butyl Acetate (TBAC)

Dear Dr. Luo:

The Consumer Specialty Products Association, Inc. (CSPA) is a voluntary, non profit national trade association representing approximately 250 companies engaged in the manufacture, formulation, distribution, and sale of chemical specialties products for household, institutional, commercial and industrial use. CSPA member companies' wide range of products includes home, lawn and garden pesticides, antimicrobial products, air care products, industrial, automotive specialty products, detergents and cleaning products, polishes and floor maintenance products, and various types of aerosol products. These products are formulated and packaged in many forms and are generally marketed nationally.

Representing the consumer products industry, CSPA has played a primary role for more than fifteen years in the California Air Resources Board (CARB) development of regulations limiting the volatile organic compound (VOC) content of various categories of consumer products, including the latest CONS-1 rule adopted last year and receiving final approval this year. CSPA will also play an active role in assisting CARB in the development of technologically and commercially feasible new limits during the CONS-2 rulemaking later this year.

CSPA appreciates the opportunity to comment on this revised draft "Environmental Impact Statement for tertiary-Butyl Acetate" dated June 2005. For our members seeking to reformulate products to meet the ever more stringent VOC limits being adopted by CARB, it is important that sufficient reformulation options be made available, including the use of VOC-exempt solvents that are found to be negligibly reactive and of very low ozone formation potential. We therefore strongly support CARB's finding in this environmental assessment that tertiary-butyl acetate (TBAC) qualifies for VOC exemption as a negligibly reactive compound, forming, on average, less than one-half as much ozone as ethane on a per-gram basis.

Although TBAC, once exempted, could be found suitable for some uses in consumer products facing more stringent VOC limits, it is too early to know what level of use in what types of products might occur. It is also too early to know what VOCs would likely be replaced by TBAC in these products.

CSPA is concerned, however, that the draft impact statement recommends that staff 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. The draft

recommendation further states that, "If staff determines that the use of TBAC in certain products could cause unacceptable exposures, we will propose appropriate mitigation measures in the Consumer Products Regulations at the time the exemption is proposed as an amendment."

CSPA believes that this level of concern is unwarranted. Our review of the draft assessment found several factors that we believe has led to this excessive concern:

- The assessment fails to adequately consider the significant scientific evidence that neither TBAC nor its metabolite, tertiary-butyl alcohol (TBA), present carcinogenic risks in humans. The weight of the evidence demonstrates that neither TBA nor TBAC are genotoxic. There is no direct evidence of TBAC carcinogenicity, and the National Toxicology Program assays on TBA did not find clear evidence of carcinogenicity in either rats or mice.

- The risk assessment assumptions used in the draft assessment greatly overestimates any potential cancer risk that could exist. We believe any such assessment should treat TBA only as a threshold carcinogen, with potency based on the female mouse kidney response, not the irrelevant male rat kidney response. The grossly conservative assumption that 100% of TBAC that is inhaled is absorbed and converted to TBA also overstates the potential risk.

- The outdoor air modeling methodology also uses many overly conservative default assumptions that serve to overestimate air concentrations near consumer product use sites such as automotive maintenance and repair facilities.

CSPA therefore does not believe that any significant carcinogenic risks are likely to be presented by any potential uses of TBAC in consumer products, based on the current scientific evidence. We therefore believe that it is unnecessary to closely monitor future uses of TBAC in our products. CSPA urges CARB to proceed with approval of the VOC exemption for TBAC without undue restrictions.

CSPA once again appreciates the opportunity to comment on this draft environmental assessment. Please feel free to contact us at any time if you have any questions.

Respectfully submitted,

D. Douglas Fratz
Vice President, Scientific & Technical Affairs

cc: CSPA Air Quality Special Committee and Reactivity Task Force

August 1, 2005

Dr. Dongmin Luo, Ph.D., P.E.
Research Division
California Air Resources Board
1001 I Street
Sacramento, California 95812

Dear Dr. Luo:

I am writing on behalf of the National Paint and Coatings Association (NPCA) to provide comments on the June 2005 staff report "Environmental Impact Assessment of tertiary-Butyl Acetate (TBAC)".

NPCA is a voluntary, nonprofit trade association representing some 350 manufacturers of paints, coatings, adhesives, sealants, and caulks; raw materials suppliers to the industry; and product distributors. As the preeminent organization representing the coatings industry in the United States, NPCA's primary role is to serve as ally and advocate on legislative, regulatory and judicial issues at the federal, state, and local levels. For over two decades, the NPCA and its member companies have been extensively involved in the development of numerous clean air regulations at the federal, state and local levels.

NPCA and its members have been actively involved in the efforts to have TBAC exempted from VOC regulations. Few industry groups appreciate its importance as much as our members who must reformulate their products to meet ever stricter VOC standards in California. While not a panacea for all reformulation challenges, TBAC is seen as a critically important tool in helping our industry meet California's clean air requirements. We, therefore, wholeheartedly endorse the decision to add TBAC to California's list of VOC-exempt compounds.

However, like Lyondell, an NPCA member and the manufacturer of TBAC, 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 whether 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.

We do know from our members that previous delays in exempting the material have hindered R&D efforts and product introductions nationwide. We also believe that CARB's letter to EPA expressing its concerns was a factor in the unusually lengthy Federal exemption process for TBAC. We are concerned that the uncertainty of this qualified exemption will likely have a similar impact at the State and district levels.

Nonetheless, NPCA, Lyondell, and our membership will continue to do our utmost to resolve any continuing reservations as CARB and the air districts quickly move forward to exempt TBAC in all product categories where it can be of use.

Sincerely,

Jim Sell
Senior Counsel

cc: Richard Corey