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Re: Draft Hot Spots Cancer Inhalation Unit Risk Factors for p Chloro-α,α,α-trifluorotoluene (p-chlorobenzotrifluoride, PCBTF) - October 18, 2019

The American Coatings Association (ACA) offers the following comments on the Office of Environmental Health Hazard Assessment (OEHHA) draft document, titled "p-Chloro-α,α,α-trifluorotoluene (p-Chlorobenzotrifluoride, (PCBTF) Cancer Inhalation Unit Risk Factor Technical Support Document for Cancer Potency Factors: Appendix B (October 2019).[1] The ACA has serious concerns with the draft document and believes that it should be revised before review by the Scientific Review Panel. In several key aspects of the draft document, it appears that OEHHA did not use the best available science, failed to evaluate all of the available data, and did not employ generally accepted methods, as discussed in further detail throughout this letter.

Because of the highly technical nature of the OEHHA (2019) draft document, it should be noted that the ACA worked closely with consultants from Ramboll US Corporation to review the draft document and prepare these comments.

SUMMARY

OEHHA should revise the draft document because the evaluation contained within it demonstrates that, in key places, OEHHA did not employ the best available science, it did not

[1] ACA is a voluntary, nonprofit trade association working to advance the needs of the paint and coatings industry and the professionals who work in it. The organization represents paint and coatings manufacturers, raw materials suppliers, distributors, and technical professionals. ACA's mission includes programs and services that support the coatings industry's commitment to environmental protection, sustainability, product stewardship, health and safety, corporate responsibility, and the advancement of science and technology. Additional information is available on the ACA website, https://www.paint.org.

account for all of the data, and it did not rely on generally accepted methods. Specifically, the ACA has the following concerns:

- In the estimation of the Cancer Slope Factor (CSF) or Inhalation Unit Risk (IUR) for PCBTF, OEHHA (2019) has applied linear low-dose extrapolation. This default assumption is incorrect, because it assumes that PCBTF is mutagenic. The available data show that PCBTF is not mutagenic. The weight of evidence also demonstrates that PCBTF and its metabolites are not genotoxic. OEHHA's approach is inconsistent with conclusions reached by NTP (2018), which found that PCBTF is neither mutagenic nor more generally genotoxic. OEHHA (2019) itself observed that "All studies of PCBTF mutagenicity have reported negative findings." In the absence of data supporting mutagenicity, it is inappropriate for OEHHA to use a linear no-threshold approach to derive a CSF/IUR for PCBTF. Instead, OEHHA should have used a nonlinear approach.[2] OEHHA's use of linear, low-dose extrapolation likely overestimated the potential carcinogenic risk of PCBTF to humans, if any such risk actually exists. [3]
- OEHHA (2019) concluded that the mechanisms by which PCBTF causes tumors are not known. However, for the mouse liver tumors -- the endpoint upon which the recommended IUR is based -- OEHHA gave no consideration to the mode of action proposed by the National Toxicology Program (NTP 2018) for these tumors. Moreover,

[2] The existence of a threshold for effects should be welcome news to all stakeholders, including regulators and public health advocates. Even if one accepts OEHHA's assertion that PCBTF poses a risk of cancer to humans, if the risk of those effects only occurs above a certain threshold -- which could possibly be at a level that is above most, if not all, levels of human exposure -- then health protective measures can be clearly identified and communicated to users of the chemical, while also enabling the public to continue receiving the health benefits of reduced ground level ozone that is achieved through industry's use of this chemical as an "exempt" solvent in coatings. Results from available worker studies provide evidence of exposures for which higher than expected rates of the types of cancers observed in animals following exposure to PCBTF were not observed in the workers (Occidental Chemical Corporation 1992). This resulted despite PCBTF exposure having occurred in combination with more than 80 other chemicals and workers potentially having elevated levels of exposure compared to traditional consumers. Currently, there are no viable alternatives available to replace PCBTF where it is used as an exempt solvent. Hence, any regulatory action taken on this chemical must be based on an accurate, carefully calibrated and data-driven assessment of the potential risks to human health, if any. Over-regulating this chemical to avoid an uncertain hazard (i.e., potential health effects in humans) will only bring about the near-certain public health impacts of increased ground level ozone. If OEHHA questions this assertion, it should consult with CARB and other air regulators throughout the state.

[3] The ACA continues to assert that the data are insufficient to support listing PCBTF under Proposition 65. As indicated in its letter to Dr. Lauren Zeise, Ph.D., dated September 19, 2019, the association has chosen not to seek judicial review of the listing at this time. OEHHA should not interpret the ACA's decision as agreement with the PCBTF listing. As discussed in it comments to the proposed listing, the association believes that the PCBTF listing is inconsistent with the applicable legal and factual requirements for listing. ACA reviewed OEHHA's response to the Association's comments and did not find it persuasive.

it appears that OEHHA made no attempt to evaluate the available toxicity data relevant to understanding the mode of action. Had OEHHA undertaken such a review, it would have discovered that the available data for PCBTF are consistent with NTP's (2018) proposed mode of action and that tumors occurring in rodents by this mode of action are not relevant to human health. As such, the mouse liver tumor data should not be used to derive the CSF/IUR. Use of these data likely overestimates the potential for human health risk.

- When estimating the recommended IUR for PCBTF, OEHHA (2019) does not appear to have relied upon generally accepted methods for selecting a dose-response model. In addition, it appears that OEHHA (2019) failed to adequately assess the goodness-of-fit of the models it applied to the data. The agency also failed to use generally accepted time-to-tumor models to adjust for survival. These failures may have resulted in the agency over- or under-estimating the potential potency of PCBTF.

DISCUSSION

I. OEHHA Is Not Using the Best Available Science to Derive the CSF/IUR – Specifically, Assuming the Mutagenicity of PCBTF and Low-Dose Linearity for Cancer Risk is Incorrect.

In the estimation of the CSF or IUR for PCBTF, OEHHA (2019) has assumed linear low-dose extrapolation. This default assumption is incorrect. The available data show that PCBTF is not mutagenic. The available data also demonstrate that PCBTF and its metabolites are not genotoxic. OEHHA's approach is inconsistent with conclusions reached by NTP (2018), which found that PCBTF is neither mutagenic nor more generally genotoxic. OEHHA (2019) itself observed that "All studies of PCBTF mutagenicity have reported negative findings." In the absence of data supporting mutagenicity, it is inappropriate for OEHHA to use a linear no-threshold approach to derive a CSF/IUR for PCBTF. Instead, OEHHA should have used a nonlinear approach, as explained further in the paragraphs below.

The linear no-threshold methods that OEHHA (2019) used assume that there is a risk of cancer with any exposure to PCBTF. This assumption is premised on exposure to a chemical causing alterations in the DNA (e.g., mutagenicity) that are transmitted to successive cell generations. OEHHA's (2009) Technical Support Document for Cancer Potency Factors, which sets forth the methods OEHHA uses to derive IURs and CSFs, states:

> "The procedures used to extrapolate low-dose human cancer risk from animal carcinogenicity data assumed that a carcinogenic change induced in a cell is transmitted to successive generations of cells descendants, and that the initial change in the cell is an alteration (e.g., mutation, rearrangement, etc.) in the cellular DNA. Non-threshold models are used to extrapolate to low dose human cancer risk from animal carcinogenicity data." (Emphasis added.)

However, when a chemical is not mutagenic – as is the case with PCBTF – the application of non-threshold or linear approaches are inappropriate. This opinion is shared by other authorities such as the United States Environmental Protection Agency (USEPA). OEHHA (2009) refers to and relies on the USEPA (2005) Cancer Guidelines for additional details on the dose-response modeling used for estimation of CSFs/IURs. The USEPA (2005) guidelines indicate that linear extrapolation should be used for agents that are DNA-reactive and have direct mutagenic activity. However, when a chemical is not mutagenic – as is the case with PCBTF -- USEPA (2005) provides guidelines for a nonlinear approach.

When evaluating the potential for mutagenicity of PCBTF or for any compound, it is important to understand the differences between mutagenicity and genotoxicity, two terms which are often used interchangeably. Mutagenicity refers to direct damage to DNA that can be heritable or passed on from cell to cell, while genotoxicity covers a broader range of endpoints that are not transmissible from cell to cell or generation to generation. In other words, if a chemical is mutagenic, it is also genotoxic, but a chemical could be genotoxic without being

mutagenic. Assays that measure mutagenicity are also considered measures of genotoxicity; however, all assays that measure genotoxicity are not indicative of mutagenic potential. Examples of assays that are measures of genotoxicity include unscheduled DNA synthesis (UDS), sister chromatid exchanges (SCEs) and DNA strand breaks. While UDS and SCEs are measures of genotoxicity, they are not measures of mutagenicity because the endpoints measured are not transmissible from cell to cell or generation to generation (Preston and Hoffman 2013). These differences need to be kept in mind when evaluating the data that NTP and others have generated in determining the potential mode of action of PCBTF and the relevant dose-response modeling approach.

In reviewing the available genotoxicity data for PCBTF, NTP (2018) concluded that PCBTF "may not directly cause mutations and initiate carcinogenesis," and that it "may be capable of inducing chromosomal damage at high levels of inhalation exposure in male mice," but that the mode of action for the carcinogenicity observed in rats and mice is "unlikely to be driven by genotoxicity." In other words, NTP (2018) found that PCBTF is neither mutagenic nor genotoxic. These NTP (2018) conclusions are critical as the results from this study are the only ones relied upon by OEHHA (2019) for the estimation of an IUR for PCBTF. NTP (2018) also is the authoritative review that initiated the Proposition 65 listing of PCBTF as a potential carcinogen.

In the Public Review Draft of the PCBTF IUR factor, OEHHA (2019) provides a summary of all available genotoxicity data for PCBTF from published and unpublished studies considered by OEHHA. (*See* Table 4.) The evidence provided in this table demonstrates that the weight of evidence for the genotoxicity and mutagenicity of PCBTF is negative. OEHHA (2019) itself concluded that "All studies of PCBTF mutagenicity have reported negative findings."

The limited positive evidence summarized in Table 4 has uncertainties related to the association between PCBTF administration and the endpoints observed. In addition, the *in vivo* and *in vitro* assays reported only provide measures of potential genotoxicity, but not mutagenicity. Each measure has serious limitations, as discussed below.

The only positive evidence of *in vivo* genotoxicity (and not mutagenicity) provided in Table 4 of OEHHA (2019) is micronucleus formation reported in NTP (2019). The increase in the incidence of micronuclei is only reported in male mice at the highest concentration of PCBTF tested (2000 ppm), with no similar increase noted in female mice or in male or female rats tested at similar concentrations. Further, the concentrations at which micronucleus formation was observed did not correspond with the concentrations at which tumors were observed in the NTP (2018) study, suggesting micronuclei are not part of the mode of action for the observed tumors in rodents. Considering the results from this *in vivo* assay, NTP (2018) concluded that genotoxicity is not part of the mode of action for the tumors observed in rodents following PCBTF exposure.

Regarding *in vitro* measures of potential genotoxicity, only two out of twenty entries in Table 4 of the IUR documentation provided evidence of genotoxicity *in vitro* (Benigni et al. 1982; Litton Bionetics 1979). The *in vitro* assays reported in these studies are the UDS assay in human embryonic epithelial cells (Benigni et al. 1982) and the SCE assay conducted in mouse lymphoma cells (Litton Bionetics (1979b). In addition to being nearly forty (40) years old, these assays have other serious limitations.

Although Benigni et al. (1982) reports a significant increase in the incidence of UDS following administration of the 3 highest concentrations of PCBTF (1, 2 and 10 µl/ml) administered to cells from human skin and muscle explants, the incidences of UDS did not increase with increasing concentration. This may be related to the potential cytotoxicity of PCBTF. Importantly, as noted in a separate entry in Table 4 of OEHHA (2019), Benigni et al. (1982) also provides negative results for mutagenicity in the Ames assays. Benigni et al. (1982) reported that the lack of mutagenicity observed in the Ames assay they conducted was consistent with a lack of mutagenicity of PCBTF in a separate study in which Wistar rats were administered 100 mg PCBTF/kg bw/day for three days.

The Litton Bionetics (1979) study, in addition to being nearly 40 years old, is an unpublished report that provides the results of a SCE assay conducted in mouse lymphoma cells. While the frequency of SCEs reported is statistically significantly increased compared to the solvent control (DMSO), the frequency following administration of PCBTF is much closer to the solvent control incidences of SCE and much lower than those reported with the positive control (EMS). This would suggest only weak genotoxic potential for PCBTF, at best. In addition, as with the Benigni et al. (1982) study, the incidence of the measurement of genotoxicity, SCE/chromosome or SCE/cell, does not increase with increasing concentrations of PCBTF. This adds uncertainty to the association between PCBTF and the genotoxicity reported. As noted in Preston and Hoffman (2013), the results from both the UDS and SCE *in vitro* assays provide evidence of potential genotoxicity, but not mutagenicity.

Lastly, in addition to evaluating the potential mutagenicity and genotoxicity of PCBTF, OEHHA considered metabolites of PCBTF. In its report, OEHHA (2019) noted concern regarding the generation of a reactive and genotoxic metabolic intermediate that could potentially be of concern in determining the mutagenic potential of PCBTF. However, the potential for a mutagenic metabolite is not supported by the available evidence provided in Table 4 of OEHHA (2019) – the results from all mutagenicity assays incorporating metabolic activation are negative. Litton Bionetics (1979) provides results from the SCE assay in the presence of metabolic activation. The authors characterize the results of the assay as erratic. While three of the five dose levels yielded frequencies that were significantly greater than the solvent control frequency, there were concentrations, including the highest concentration tested, that failed to show any significant effect. The authors considered the results of the assay as positive but noted the lack of a clearly defined dose-response.

Accordingly, based on the evidence provided in Table 4 of OEHHA (2019), there is no evidence that PCBTF is mutagenic. There is, at best, limited evidence *in vitro* that PCBTF is genotoxic (Benigni et al. 1982: Litton Bionetics 1979); however, there is uncertainty in the results from these studies because there is no clearly defined association with exposure to PCBTF. Considering the uncertainties in the available positive assays, it is important to consider NTP's conclusions that PCBTF is not genotoxic or mutagenic and therefore, the assumption of low-dose linearity in estimating the potential carcinogenic risk from exposure to PCBTF is incorrect. As such, OEHHA should abandon use of its linear, no-threshold approach and instead derive a CSF/IUR using a threshold model. The available data suggests that there is a threshold below which exposure to PCBTF is without an appreciable increase in the risk of cancer.

II. OEHHA Did Not Consider All Available Data For the Mouse Liver Tumors – Specifically, OEHHA Did Not Conduct a Proper Assessment of the Mode of Action Identified by NTP, which is Supported by Available Data.

OEHHA (2019) concluded that the mechanisms by which PCBTF causes tumors are not known. However, for the mouse liver tumors -- the endpoint upon which the recommended IUR is based -- OEHHA gave no consideration to the mode of action proposed by NTP (2018) for these tumors. Moreover, it appears that OEHHA made no attempt to evaluate the available mode of action data. Had OEHHA undertaken such a review, it would have discovered that the mode of action proposed by NTP (2018) for liver tumors in rodents is not relevant to human health. As such, the mouse liver tumor data should not be used to derive the CSF/IUR. A discussion of the available data is set forth below.

In the discussion of the NTP (2018) study, NTP offers the following conclusions related to the mode of action for mouse liver tumors:

- There is evidence that PCBTF exposure can lead to cytochrome P4502B (CYP2B) induction in the liver of rodents (Pelosi et al. 1998).
- Other cytochrome isoforms evaluated (e.g., cytochrome P4502E) showed higher activity in animals exposed to PCBTF; however, the strongest induction was CYP2B.
- CYP2B activation via the constitutive androstane receptor (CAR) is a known mechanism for tumor promotion activity in the liver of rodents (Sakamoto et al. 2013).
- Liver weights and nonneoplastic lesions observed in the NTP 3-month and 2-year studies are also consistent with a potential CAR-mechanism (Bucher et al. 1994; Parkinson et al. 2006).

Based on NTP's conclusion that the increased incidence of hepatocellular carcinomas reported in male and female mice following inhalation exposure to PCBTF could occur through a potential CAR-mechanism of action (MOA), Ramboll scientists conducted a review of the available results from toxicity studies for PCBTF. NTP (2018) suggested a CAR mode of action for the observed mouse liver tumors based on: (1) the observation of key events for the CAR-

MOA including reported increases in CYP2B activity in rats following oral exposure to PCBTF (Pelosi et al. 1998), (2) concentration-related increased liver weights in mice exposed to PCBTF via inhalation for 3 months (NTP 2018), and (3) the consistent evidence from standard *in vitro* assays that PCBTF is not genotoxic (NTP 2018). The key events focused on by NTP (2018) are also consistent with an adverse outcome pathway (AOP) for CAR activation available on the AOP Wiki (Figure 1), which is hosted by the Society for the Advancement of Adverse Outcome Pathways (SAAOP) and endorsed and supported by the US Army Engineer Research & Development Center (ERDC), the USEPA, the Organisation for Economic Co-operation and Development (OECD), the NTP and the European Commission (EC).

The data for PCBTF follow a familiar pattern for other well-known CAR-mediated chemicals, such as phenobarbital. Phenobarbital induced hepatocellular carcinomas in rodents are reported to occur through a CAR-MOA (Holsapple et al. 2006). Phenobarbital has been well-studied and the mode of action for rodent hepatic tumors well established; therefore, potential modes of action of other chemicals are often compared to the evidence for phenobarbital to establish the potential of a CAR-MOA. Holsapple et al. (2006) reports that phenobarbital is the prototype rodent hepatocarcinogen that induces liver tumors through the activation of CAR (a non-genotoxic mechanism) with associated key events that include increased cell proliferation, inhibition of apoptosis, hypertrophy, and the development of altered hepatic foci (Holsapple et al. 2006). The authors conclude that for compounds for which the data are consistent with a phenobarbital-like or CAR-MOA, the carcinogenic response is <u>not</u> relevant to humans. Evaluations for other compounds have concluded that rodent hepatocellular tumors occurring by the CAR-MOA are considered not relevant to human health (Elcombe et al. 2014; Yamamoto et al. 2004; Holsapple et al. 2006; Yamada et al. 2009).

The results from Ramboll's review of the toxicity data for PCBTF provide evidence of dose-response relationships (both oral and inhalation) between PCBTF and multiple key events and associative events in an established adverse outcome pathway for CAR-MOA for the induction of hepatocellular adenomas and carcinomas in rodents (Peffer et al. 2016). These key events and associative events are also consistent with the proposed AOP for CAR (Peffer et a. 2016) and those associated with phenobarbital-induced liver tumors in rodents (Holsapple et al. 2006; Elcombe et al. 2014; Yamamoto et al. 2004; Numazawa et al. 2005; Yoshiniari et al. 2001; Waxman and Azaroff 1992), all of which are <u>not</u> relevant to human health.

Accordingly, OEHHA's decision to rely on the male mouse liver tumors reported in the NTP (2018) study to establish the potential for carcinogenicity in humans is <u>not</u> based on a critical review of the available science for PCBTF. The available science for PCBTF is consistent with a mode of action (CAR activation) proposed by the NTP (2018) for male mice liver tumors (the endpoint relied upon for the OEHHA recommended IUR). Further, tumors occurring by this mode of action in rodents are <u>not</u> relevant to human health. As such, OEHHA should either abandon use of the mouse liver tumor data when developing the CSF/IUR or conduct a thorough analysis of the available data to evaluate the CAR mode of action and the

relevance of the mouse liver tumor data to human health. OEHHA should not proceed any further with the draft CSF/IUR without making these changes.

III. OEHHA Did Not Use Generally Accepted Modeling Approaches – Specifically, the Agency Relied Upon Draft Guidance, Ignoring OEHHA's Own Peer-Reviewed Final Guidance.

When estimating the recommended IUR for PCBTF, OEHHA (2019) does not appear to have relied upon generally accepted methods for selecting a dose-response model. In addition, it appears that OEHHA (2019) failed to adequately assess the goodness-of-fit of the models it applied to the data. The agency also failed to use generally accepted time-to-tumor models to adjust for survival. These failures may have resulted in the agency over- or under-estimating the potential potency of PCBTF.

When selecting a dose-response model, OEHHA (2019) appears to have used methods taken from a 2014 draft operating procedure for USEPA subcontractors (reference to USEPA 2016 is incorrect in the IUR documentation) that was never finalized. These methods are inconsistent with those found in USEPA's well-established final BMDS Guidance (2012), as well as the OEHHA (2009) Technical Support Document. As noted previously, for detailed methods on dose-response, OEHHA (2009) defers to USEPA (2005) Guidelines for Carcinogen Risk Assessment.

In selecting the model for estimation of the IUR, a draft operating procedure (USEPA 2014) was cited by and relied on by OEHHA (2019) to choose the number of stages for cancer modeling. The approaches in that draft document are inconsistent with the well-established USEPA (2012) BMDS Guidance which has been through inter- and intra-agency review, an external peer review and a public workshop. This 2012 USEPA BMDS Guidance is recommended on the USEPA website accompanying the BMDS model and "provides guidance on the application of the benchmark dose approach for determining the point of departure for health effects data." Therefore, USEPA's (2012) BMDS Guidance represents accepted scientific methods across the scientific community whereas the draft operation procedure that OEHHA relied upon does not.

Assessing the goodness-of-fit of a model to the data is critical in selecting a benchmark dose and the first item listed in both Standard Operating Procedure for USEPA subcontractors (USEPA 2014) and USEPA BMDS Guidance (USEPA 2012) is reliance upon the Akaike's Information Criterion (AIC) for comparison across models. The AIC is not reported or relied upon for modeling decisions in the OEHHA (2019) Public Review Draft of the documentation of the IUR for PCBTF. OEHHA (2019) only reported p-values to characterize goodness-of-fit. However, according to the USEPA (2012) BMDS Guidance, goodness-of fit values, such as p-values, are not designed to compare results across models. Therefore, the lack of consideration of the AIC indicates that the fit of the models to the data has not been adequately assessed.

The method OEHHA (2019) used to adjust for differential early mortality or significant differences in survival is a crude approach and is not recommended in either the USEPA (2005) Guidelines for Carcinogen Risk Assessment or the OEHHA (2009) Technical Support Document. Rather, the application of time-to-tumor models are noted in both Guidance documents to account for significant decreases in survival. And therefore, currently accepted scientific approaches were not relied upon to adjust for survival.

The application of modeling approaches that are inconsistent with both finalized USEPA Guidelines and OEHHA Guidelines have resulted in the use of dose-response models that may not adequately characterize the available data. This may result in significant over- or underestimates of the potential potency of PCBTF. As such, OEHHA should re-evaluate the potential potency using generally accepted methods.

CONCLUSION

ACA and its members take their environmental stewardship responsibilities very seriously. PCBTF was developed as a substitute for use in ACA member products precisely because it assists in reducing the public health effects of ground level ozone. Currently, there are no viable alternatives available to replace PCBTF where it is used for this purpose. Accordingly, it is imperative that OEHHA's CSF/IUR accurately characterize the potential carcinogenicity of PCBTF, assuming there is such potential in humans. ACA urges OEHHA to revise its draft CSF/IUR before submitting it to the Scientific Review Panel. We believe the current draft document includes significant errors by not using the best available science, by failing to evaluate all available data, and by not using generally accepted methods.

Respectfully submitted,

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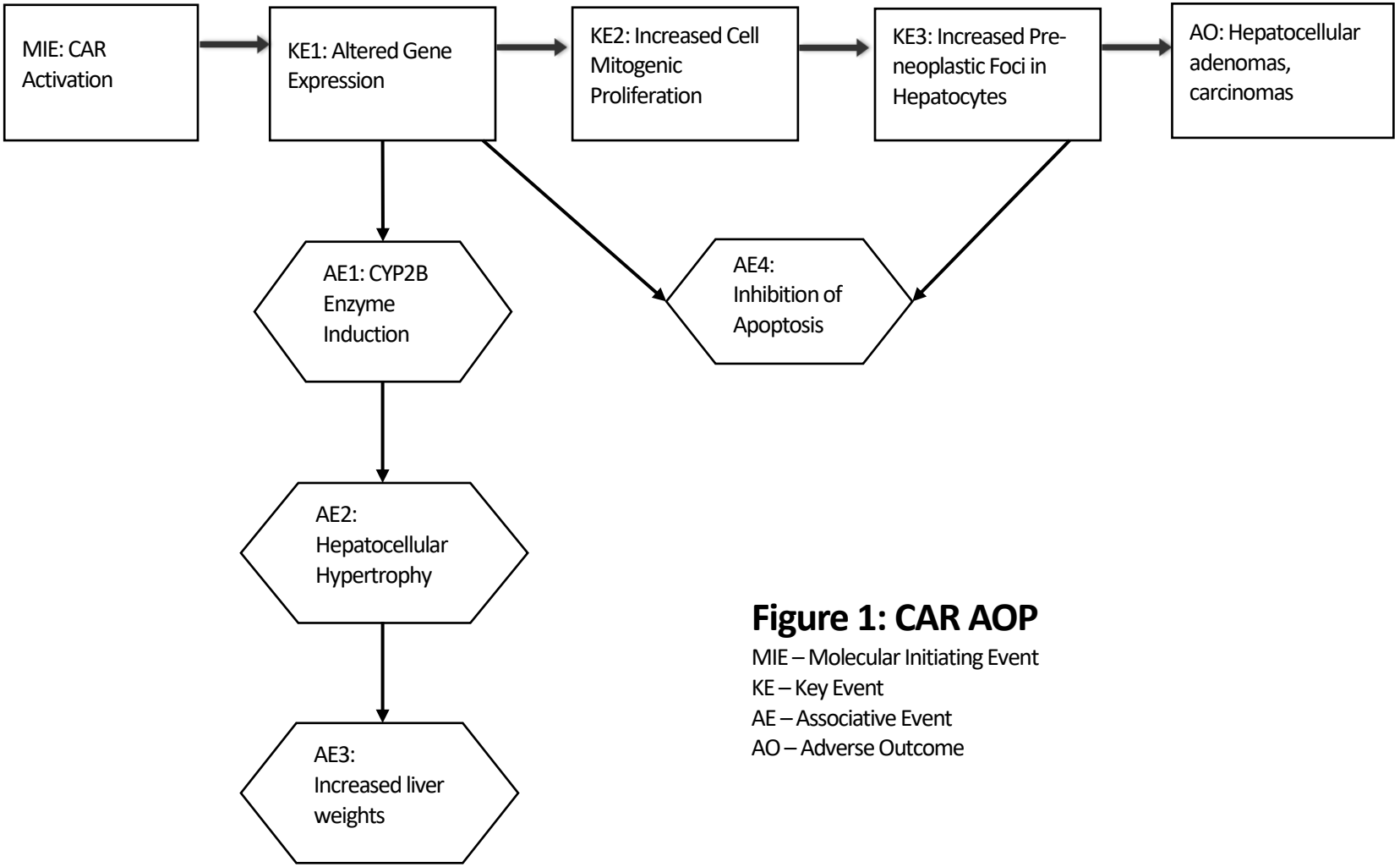

Figure 1: CAR AOP

MIE – Molecular Initiating Event
KE – Key Event
AE – Associative Event
AO – Adverse Outcome