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Subject HID – DINP

Dear Ms. Oshita

My comments below with regard to the OEHHA document "Evidence on the Carcinogenicity of Diisononyl Phthalate" will be directed to the rodent liver effects summarized in the document and the relevance of these effects to human cancer risk.

For over 35 years, my laboratory has been involved in understanding the mechanisms of hepatic chemical carcinogenesis. A specific interest of my laboratory has been to investigate the pathological, cellular and molecular mechanisms by which nongenotoxic agents such as the peroxisome proliferators (PPAR alpha activating compounds) induce neoplastic development in the rodent liver.

Overview

In the 1970s, a number of published reports linked the induction of liver tumors in rodents with a variety of chemicals that increased the number and size of peroxisomes (peroxisome proliferation) (Rao & Reddy, 1996). Peroxisomes are subcellular organelles found in almost all eukaryotic cells involved in (among many functions) long chain fatty acid catabolism through b-oxidation. In 1990, the PPAR alpha gene and PPAR alpha encoded protein was described by Issemann & Green (1990). It was subsequently determined that PPAR alpha belongs to the nuclear receptor superfamily that includes the steroid hormone and retinoic acid receptors. Other members of the PPAR subfamily include PPAR alpha, PPAR beta and PPAR gamma, which have different tissue distributions, expression patterns, ligand specificity and biological functions. Further understanding of the PPAR alpha was facilitated by the development of the PPAR alpha -null mouse in 1995 (Lee et al., 1995). The hepatic cellular and molecular events through which activators of PPAR alpha induce rodent liver tumors have been extensively studied. These cellular events including regulation of genes involved in lipid metabolism, peroxisome proliferation, hepatomegaly, alteration in hepatocyte function, and liver tumor induction. These hepatocyte effects are directly linked to the activation of PPAR alpha since these changes are not seen in PPAR alpha-null mice treated with PPAR alpha activators (Corton, 2010). Activation of PPAR alpha does occur in humans and is the basis for the beneficial pharmacological effects of hypolipidemic fibrates. However, PPAR alpha mediated gene activation in humans and non-human primates produces only a subset of the liver responses observed in mice and rats after treatment. There is no evidence that human PPAR alpha regulates genes involved in

cell growth. In further support of the difference between rodents and primates, in PPAR alpha-null mice in which the human PPAR alpha gene has been expressed (PPAR alpha 'humanized'' mice), no increase in gene expression associated with increases in hepatocyte proliferation or growth are seen following exposure to PPAR alpha activators. However, these PPAR alpha ''humanized'' mice maintain the regulation of genes involved in lipid homeostasis (Cheung et al., 2004; Yang et al., 2008).

Mode of action (MOA) framework

The revised US EPA cancer risk assessment guidelines (US EPA, 2005) encouraged the use of mechanistic data in Mode of action (MOA) analysis for risk assessment of potential human carcinogens. A framework to perform a MOA analysis and determine human relevance (HR) analysis cancer endpoints based on scientific evidence has been developed (Boobis et al., 2006; Meek et al., 2003; Seed et al., 2005). The MOA framework provides for transparency in evaluating the concerning weight of evidence for the relevance of a MOA to humans. The MOA is defined as a biologically plausible sequence of key events, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes and resulting in an observed effect that is supported by experimental mechanistic data. The analysis of the MOA for cancer determines the linkage between a postulated key event and the formation of the tumor with respect to: (1) strength, consistency and specificity of the association, (2) temporal relationships between the key events and the end point (tumors), (3) the dose–response aspects of the key events, biological plausibility and coherence of the key events, and (4) consideration of possible alternative MOAs (Boobis et al., 2006, Meek et al., 2003; Seed et al., 2005).

In 2003, a MOA was developed for PPAR alpha activating rodent liver carcinogens (Klaunig et al., 2003). In this PPAR alpha MOA , 5 key events for the induction of liver tumors in rats and mice by PPAR alpha activating compounds were defined. In Key Event 1, the PPAR alpha agent activates PPAR alpha; In Key Event 2, activation of the receptor regulates the transcription of genes involved in peroxisome proliferation, cell cycle/apoptosis and non-peroxisomal lipid metabolism (divided into events 2a, 2b and 2c, respectively). In Key Event 3, this modification of gene expression produces changes in peroxisome proliferation (Event 3a) and cell proliferation and/or apoptosis (Event 3b) and lipid metabolism (Event 3c). In Key Event 4, suppression of apoptosis and/or stimulation of cell proliferation allows for preneoplastic cells to proliferate, giving rise to preneoplastic foci and ultimately to tumors via further clonal expansion (Key Event 5). Associated events, not causal, include alteration in gap junction intercellular communication, increases in oxidative stress, and activation of Kupffer cells. The conclusion of the 2003 manuscript was that the rodent PPAR alpha MOA for liver tumors <u>was not likely relevant to humans.</u>

In the years since the original publication of this MOA for PPAR alpha activators, the published literature has supported this MOA (Corton, 2010). In particular, studies examining receptor activation, PPAR alpha-dependent mechanisms of hepatocellular proliferation and PPAR alpha humanized mouse models have confirmed the causal role of PPAR alpha in the development of the rodent liver tumors. As such a new review panel was convened to revisit the proposed MOA from the Klaunig manuscript given the significant amount new reported studies on PPAR alpha. The report of this panel has been published (Corton et al 2013). After taking into account the new results published since publication of the original MOA for PPAR alpha (from 2003), the 2013 panel concluded that the causal key events defined in the earlier MOA for PPAR alpha liver tumor induction were the same with the exception of including as a first key event the metabolism (if required) of the parent compound to an active PPAR alpha activating form. The remaining key events include activation of PPAR alpha (event 2), induction of cell growth (event 3), selective clonal expansion of preneoplastic live foci (event 4) and formation of liver tumors in rats and mice (events 5). The conclusion of the 2013 panel was that the rodent PPAR alpha MOA for liver tumors <u>was not relevant/not likely</u> to humans.

Discussion and Clarification of Issues rose in the OEHHA document "Evidence on the Carcinogenicity of Diisononyl Phthalate".

Specific comments regarding the conclusions in the OEHHA DINP document reached include:

Page 52

Ito et al. (2007) found that exposure of SV129-derived PPARα-null mice to 100 or 500 ppm DEHP in the diet for up to 22 months resulted in the induction of liver tumors in those mice, with a significant trend for dose-response. These data indicate that PPARα agonists may induce liver tumor by a mechanism independent of PPARα activation.

Increases in hepatocyte proliferation were shown to be PPAR alpha-dependent. Wild-type but not the PPAR alpha -null mice showed increases in hepatocyte proliferation (Laughter et al., 2004; Peters et al., 1998; Valles et al., 2003). Suppression of apoptosis occurred in hepatocytes from wild-type but not in hepatocytes rom PPAR alpha -null mice (Hasmall et al., 2000a). Chronic treatment with WY or bezafibrate produced hepatocellular neoplasia in 100% of wild-type mice but did not significantly increase the number of liver tumors in PPAR alpha -null mice (Hays et al., 2005; Peters et al., 1997). These two studies provide strong support for the causal role of PPAR alpha activation in the rodent carcinogenesis of PPAR alpha activators. The role of PPAR alpha in rodent liver tumor induction has been challenged by the observation of increases in liver tumor induction in PPAR alpha -null mice by DEHP (Ito et al., 2007). . In this Ito et al study, wild type and PPAR alpha -null mice were exposed to relatively low doses (0.01% or 0.05%) of DEHP in the diet for 22 months (Ito et al., 2007). The authors claimed that the incidence of liver tumors was higher in PPAR alpha -null mice exposed to 0.05% DEHP (25.8% incidence) than in similarly exposed wild-type mice (10.0% incidence), suggesting that the DEHP induced hepatic tumors were independent of PPAR alpha (Guyton et al., 2009). Several points can be made to counter the argument that the Ito et al. (2007) study provides proof to discount the PPAR alpha MOA as described by Klaunig et al. (2003) and Corton et al (2013). These include: 1) The Ito et al. (2007) study combined different types of liver tumors in their analysis (hepatocellular adenomas, carcinomas and cholangiocellular carcinomas), a non-standard method of summarizing tumor response (Thoolen et al., 2010), leaving open the possibility that the increase in hepatocellular tumors reported in the PPAR alpha-null mice was actually not statistically significant. 2) There is strong evidence that the tumors in PPAR alpha null mice arose through a mechanism that is different from the one that produces liver tumors in wild-type mice. DEHP-treated wild type and PPAR alpha -null mice did not produce equivalent levels of tumor induction. There was no statistically significant increase in any type of liver tumor in wild-type mice in this study under the treatment conditions, indicating the biological effects of DEHP treatment were not equivalent in wild-type and PPAR alpha –null mice. 3) Additionally, growth control genes were altered in PPAR alpha-null mice but not in wild-type mice at equivalent doses.

Page 52

Yang et al. (2007) developed LAP-VP16PPARα transgenic mice (from a wild-type SV129 mouse) transfected with a mouse PPARα receptor fused to the viral transcriptional activator VP16 under the control of the liver-enriched activator protein (LAP). These mice constitutively expressed activated PPARα in hepatocytes in a targeted manner. The authors then used these mice to study whether the activation of PPARα in hepatocytes only is sufficient to induce liver tumors. The LAP-VP16PPARα mice demonstrated peroxisome proliferation (including increased PCoA activity) and hepatocyte proliferation at 8 - 10 weeks of age. However, no liver tumors were noted in more than 20 LAP-VP16PPARα mice at 11 months of age. In contrast, wild-type mice fed 0.1% Wy-14,643 in the diet for 11 months developed hepatocellular carcinomas (exact number of tumor-bearing animals not provided by authors). These data indicate that PPARα activation by itself is not sufficient to induce hepatocarcinogenesis.

It is important to point out a limitation to the transgenic VP16PPARa fusion protein used in the Yang et al (2007) study. While endogenous PPAR alpha is transcriptionally activated by the molecular events seen with most nuclear receptors, the VP16PPARa fusion protein is activated by a viral transactivation domain that produces several distinctly different effects including protein-protein interactions with transcription factors TFIIA, TFIIB, the TATA-binding protein, TAFII40 components of TFIID and RNA polymerase (Hagmann et al., 1997). Other studies that have looked at the effect of VP16 fusion proteins have found that while the VP16 fusion protein retains the ability to trans activate, it does not induce the phenotypes observed through endogenous pathways (Schwarz et al., 1992). Therefore the VP16PPARa fusion protein does not induce all of the changes necessary for tumorigenesis. This concern is further supported by the follow up study by Qu et al., 2010).

Page 54 and 55

The PPARα liver tumor MOA hypothesis proposed by Klaunig et al. (2003) identifies increased hepatic cell proliferation and perturbation of apoptosis as PPARα-dependent causal events leading to tumor formation. However, the data on short-term induction of hepatocellular proliferation in DINP-exposed B6C3F1 mice are inconsistent, and long- term hepatocellular proliferation has not been shown to occur in DINP-exposed rats.

There is confusion on the role of cell proliferation (more specifically cell growth modulation taking into account the balance of cell death (apoptosis and cell division) in the induction of liver tumors in rodents by chemical agents. The common method to measure cell proliferation (DNA synthesis) is the utilization of immunohistochemical markers (PCNA or BRDU). Using these probes a percent of cells undergoing DNA synthesis can be scored. Most agents functioning through receptor mediated non genotoxic modes of action display a transient increase in DNA synthesis in the liver after 1 to 2 weeks of treatment which reverts to control levels at later times. Of central importance the defined MOA is the long term induction of DNA synthesis in the target cell for tumor induction (the preneoplastic liver cell). Unfortunately, these cells are difficult to discern in the liver. Thus the selective clonal expansion of these preneoplastic cells through either cell proliferation and/or inhibition of apoptosis are difficult to quantitate. Using rodent liver model system my lab has been able to further define the role of the preneoplastic foci on the progression of liver tumors. (Kolaja et al 1996a; 1996b; 1976c; Isenberg et al 2001)

Page 56

Perturbation of apoptosis
Kaufmann et al. (2002) studied apoptosis (as measured by TUNEL stain labeling) in male and female B6C3F1 mice exposed to DINP in the diet at doses of 500, 1500, 4000 or 8000 ppm for either one or four weeks of exposure. Concurrent controls were provided for the four week exposure groups but not the one week exposure groups, making interpretation of the one week exposure group results problematic. The rates of hepatocellular apoptosis (assessed in zones 1, 2 and 3) were not significantly different from controls in males and females at all DINP dose levels after four weeks of DINP exposure.
In isolated primary F344 rat hepatocytes exposed in vitro to the DINP metabolite MINP at concentrations ranging from 150 to 250 μM, transforming growth factor β1-induced apoptosis was significantly suppressed (Shaw et al., 2002).

As noted above, the development of rodent liver tumors is dependent on the overall increase in selective growth of preneoplastic hepatocytes. This can occur through either and increase in cell proliferation and or a decrease in cell death (apoptosis). Depending upon the species of rodent and the carcinogen being examined, one can find in the literature references to both processes. However, the result is the same, an increase in the growth of the preneoplastic lesion.

Activation of CAR and PXR
DINP activates the human constitutive androstane receptor (CAR) and pregnane X receptor (PXR), two closely related liver-enriched nuclear hormone receptors which regulate the transcription of a number of drug-metabolizing enzymes and transporters. For example, activation of CAR and PXR results in the induction of a number of Cyp2b, Cyp2c, and Cyp3a isozymes (Hester et al., 2012).
DeKeyser et al. (2011) studied the activation of CAR and PXR by DINP using reporter transactivation assays and two-hybrid studies in COS-1 cells (studies described in Section 3.3.5). In transactivation studies, COS-1 cells were transfected with the human CAR2 transcript or the human PXR transcript. DINP displayed potent activation of the 2B6-XREM-PBREM reporter (derived from the natural CYP2B6 gene promoter) compared with the positive control through human CAR2, indicating that DINP induces CYP2B6 through CAR. DINP was a weak activator of human PXR in this system. Ex vivo studies showed that DINP treatment of primary human hepatocytes resulted in increased protein expression of the CAR and PXR inducible enzymes CYP2B6 and CYP3A4 (DeKeyser et al., 2011). Interestingly, testosterone is a substrate for both CYP2B6 and CYP3A4 (Imaoka et al., 1996).
PPARα-humanized (hPPARα) mice that express human PPARα only in the livers of PPARα-null mice were used by Ito et al. (2012) to study the differences between hepatic mouse and human PPARα and CAR activation in response to the phthalates DBP and DEHP. Twelve-week old hPPARα and wild-type mice (mPPARα; SV129 genetic background) were exposed by gavage to 0, 2.5 or 5 mmol/kg body weight DBP or DEHP in corn oil daily for two weeks. Both phthalates tested activated both PPARα and CAR in both hPPARα and mPPARα mice. However, PPARα activation was stronger in mPPARα mice than in hPPARα mice, while CAR activation was stronger in hPPARα mice compared to mPPARα mice.

In a study by Wolf et al, (2008) the PARA alpha activator PFOA was examined for its liver effects in wild-type and PPAR alpha -null mice. At the doses examined (1 and 3 mg/kg day), PPAR alpha -null mice failed to show increases in cell proliferation but displayed increases in liver-to-body weight ratios with treatment. At the highest dose of PFOA tested (10 mg/kg day) PPAR alpha -null mice showed increases in hepatocyte proliferation (Wolf et al., 2008). Microarray analysis showed that PFOA produced an alteration in 85% of the PPAR alpha dependent genes at 3 mg/kg day of PFOA. The PPAR alpha independent genes showed activation of other nuclear receptors, specifically those regulated by CAR. CAR regulates cell growth and metabolism genes including Cyp2b. The induction of the CAR gene signatures were more evident in PFOA treated PPAR alpha null mice compared to wild-type mice. These results indicate that CAR activation may occur in the transcriptional and cell proliferation effects of PFOA treated PPAR alpha null mice. In the PFOA treated wild-type mice, there were only relatively minor changes of in CAR gene expression in comparison to that seen in the PPAR alpha-dependent genes. This supports a minor role for CAR in the mechanism of PFOA induces liver tumors, with the dominant change seen with PPAR alpha related gene expression (Rosen et al., 2008a, b). A role for CAR could also provide a reason for the observed tumors in the Ito et al. study (2007). DEHP like PFOA appears to strongly activate CAR-regulated genes in PPAR alpha null mice compared to the wild-type mice (Ren et al., 2010). Again this suggests that in the absence of PPAR alpha, DEHP activates CAR and thus the CAR activation (similar to Phenobarbital) in this genetically engineered mouse may be responsible for the increase in liver tumors seen in the Ito study. Functional antagonism between transcription factors involved in opposing biological functions is a common molecular mechanism for regulation of gene expression. There is a growing body of evidence that PPAR alpha and CAR can modulate each other's activity. Thus in the absence of PPAR alpha expression, CAR expression levels can be increased (Martin et al., 2007) and phenobarbital-induced hyperplasia was greater in PPAR alpha -null mice compared to that in wild-type mice

Conclusions

As noted in the OEHHA DINP document DINP produces liver tumors in rats and mice following chronic treatment. Concomitant with the induction of liver tumors is the activation of PPAR alpha as measured directly or via surrogate markers. DINP as is evident

from the published research fits the mode of action of a PPAR alpha activating compound (Klaunig et al 2003; Corton et al 2013). As such, with regard to rodent hepatic tumors induced by DINP, it is my conclusion that the observed rodent liver tumors induced by DINP are not relevant to humans.

Sincerely

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The views and conclusion expressed in these comments are the opinion of the author and do not represent those of Indiana University.

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