

Comments on the Observations in the Liver in the Draft Technical Report (No. 576) for Trimethylolpropane Triacrylate (TMPTA)

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**Comments presented on behalf of
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Hepatic Neoplasms in B6C3F1/N Mice

Draft Conclusions

- No evidence of carcinogenic activity in male B6C3F1/N mice**
- Some evidence of carcinogenic activity in female B6C3F1/N mice based on increased incidences of uncommon malignant hepatic neoplasms (hepatoblastoma and hepatocholangiocarcinoma)**

Hepatic Neoplasms in Male and Female Mice

Male Mice	HC dermal	HC all routes	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hepatoblastoma (HB)	0/0 (0%)	50/1248 (4%)	5/50 (10%)	5/50 (10%)	4/50 (8%)	5/50 (10%)
Hepatocholangiocarcinoma (HCCC)	0/0 (0%)	10/1248 (1%)	2/50 (4%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Hepatocellular Carcinoma (HCC)	0/0 (0%)	389/1248 (31%)	22/50 (44%)	14/50 (28%)	19/50 (38%)	25/50 (50%)
Female Mice	HC dermal	HC all routes	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hepatoblastoma, Multiple (HB)	-	-	0/50 (0%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Hepatoblastoma, (includes multiple) (HB)	2/250 (0-2%)	4/1195 (0-2%)	0/50 (0%)	4/50 (8%)	0/50 (0%)	3/50 (6%)
Hepatocholangiocarcinoma (HCCC)	0/250 (0%)	0/1195 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Hepatocellular Carcinoma (HCC)	63/250 (6-46%)	144/1195 (0-46%)	12/50 (24%)	13/50 (26%)	10/50 (20%)	19/50 (38%)

3

Consider:

- **Fluoride & Liver tumors in NTP study** (TR No. 393)
 - Re-evaluate pathology and re-classify tumors from HCCC to HB to HCC
- **Hepatocholangiocarcinomas (HCCCs) In B6C3F1 Mice** (Moore et. al., Toxicologic Pathology, 2010)
 - Total 164 HCCCs from 74 two-year carcinogenicity studies
 - None were considered treatment-related
- **Hepatoblastomas (HB) in Mice in the NTP Studies** (Turusov et. al., Toxicologic Pathology, 2002)
 - Increased incidences
 - No apparent association between a specific chemical structure or a biological class of compounds and their capacity to induce hepatoblastomas
 - Combine HBs with HCCs
 - Different in mice and human

A: Not Consider HB & HCCC:

Male Mice	HC dermal	HC all routes	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hepatocellular Carcinoma (HCC)	0/0 (0%)	389/1248 (31%)	22/50 (44%)	14/50 (28%)	19/50 (38%)	25/50 (50%)
Female Mice	HC dermal	HC all routes	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hepatocellular Carcinoma (HCC)	63/250 (6-46%)	144/1195 (0-46%)	12/50 (24%)	13/50 (26%)	10/50 (20%)	19/50 (38%)

B: Consider HB & HCCC as HCC:

Male Mice	HC dermal	HC all routes	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hepatocellular Carcinoma (HCC)	0/0 (0%)	389/1248 (31%)	28/50 (56%)	18/50 (36%)	24/50 (48%)	28/50 (56%)
Female Mice	HC dermal	HC all routes	0 mg/kg	0.3 mg/kg	1.0 mg/kg	3.0 mg/kg
Hepatocellular Carcinoma (HCC)	63/250 (6-46%)	144/1195 (0-46%)	12/50 (24%)	17/50 (34%)	11/50 (22%)	20/50 (40%)

Requested Considerations for NTP and the Peer Review Panel:

- **Female B6C3F1/N Mice:**
 - **No evidence of carcinogenic activity in female B6C3F1/N mice**
 - or**
 - **Equivocal evidence of carcinogenic activity in female B6C3F1/N mice based on a marginal increase of hepatic neoplasms that may be chemical related**

Thank you!

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