April 18, 2016

Ms. Celia Peacock
CDR, United States Public Health Service
Senior Regulatory Project Manager
FDA/Center for Drug Evaluation and Research Division of Nonprescription Drug Products
Office of Drug Evaluation IV
WO22 - Room 5416 10903
New Hampshire Avenue
Silver Spring, MD 20993

**RE:** Request for Type C Meeting with the FDA Center for Drug Evaluation and Research Division of Nonprescription Drug Products, Office of Drug Evaluation IV Concerning Isopropyl Alcohol

Dear Ms. Peacock,

On behalf of the American Chemistry Council's Isopropanol Panel[1], I am writing to request a Type C meeting with the Federal Drug Administration's (FDA) Center for Drug Evaluation and Research Division of Nonprescription Drug Products' Office of Drug Evaluation IV as follow up to our October 20, 2015 meeting to further discuss the data gaps identified for isopropyl alcohol (CAS Number: 67-63-0) for use in patient preoperative skin preparations, health care personnel hand rub, and surgical hand rubs as indicated in the May 1, 2015, proposed rule *Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of the Administrative Record* (Proposed Rule)[2] .

Please find enclosed the Meeting Request Information. Please do not hesitate to contact me at 202-249-6708 or angela_lynch@americanchemistry.com to discuss meeting dates or any additional information needs. Thank you for your consideration of our request.

Sincerely,
Angela Lynch, MSPH, PhD
Isopropanol Panel Manager
American Chemistry Council
700 2nd St., NE
Washington, DC 20002

*Enclosure: Meeting Request Information Packet*

[1]The American Chemistry Council (ACC) Isopropanol Panel including The Dow Chemical Company, ExxonMobil, and Shell International, represents leading manufacturers of Isopropanol in the United States. The Panel is committed to health, safety, security and environmental issues relating to the production, transportation or use of isopropanol.
[2] 80 Fed. Reg. 25166 (May 1, 2015).

**Formal Meeting Request**
**Type C**
**Review of Data Requests/Data Gaps for Isopropyl Alcohol**
**Isopropanol Panel**

1. **Product Name.**

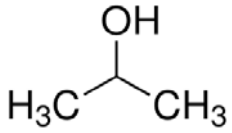
   Isopropyl Alcohol 60-91.3%

2. **Application Number.**

   Not applicable

3. **Chemical Name and Structure.**

   Isopropyl Alcohol, CAS Number 67-63-0




4. **Proposed Indication.**

   Healthcare Antiseptic for use as an active ingredient in the following:
   1) patient preoperative skin preparations;
   2) health care personnel hand rubs; and
   3) surgical hand rubs.

5. **Meeting Type**.

   Type C

6. **Statement of the Purpose and Objectives of the Meeting.**

   **a. Purpose**

   Isopropyl alcohol (IPA) and products containing IPA have been the subject of a number of interagency, intergovernmental, and agency-specific activities over a period of more than 40 years. On September 3, 2014, the FDA Nonprescription Drugs Advisory Committee (Advisory Committee) convened to discuss the topic "Pre-market safety testing framework for over-the-counter healthcare antiseptic drugs," which included a discussion on the adequacy of safety and effectiveness data for IPA (FDA, 2014). FDA's May 1, 2015, proposed rule, *Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-*

*Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of the Administrative Record* (Proposed Rule) states that additional safety and effectiveness data may be necessary to support a determination of generally recognized as safe/generally recognized as effective (GRAS/GRAE) for IPA (FDA, 2015).

The purpose of this meeting request is to follow up on the October 20, 2015, meeting to provide FDA with additional data and further discuss the data gaps identified by FDA.

**b.Objectives**

**I. Discuss Additional Data Provided for Human Pharmacokinetics and Animal ADME**:

Beginning on page 25191 of the Proposed Rule, the FDA summarizes absorption, distribution, metabolism, and disposition (ADME) studies for IPA conducted with laboratory animals and some related human ADME studies. The FDA states that "The available dermal exposure studies have demonstrated that there is some systemic exposure to isopropyl alcohol following dermal application. However, the extent of that exposure has not been fully characterized." One of the primary references for ADME dermal exposure data cited in the Proposed Rule is Boatman et al. Under the Proposed Rule, FDA states:

> In a dermal exposure study in rats, 70 percent aqueous isopropyl alcohol solution was applied to a 4.5 square centimeter area of skin on the shaved backs of male and female Fischer F–344 rats and maintained under a sealed chamber for a period of 4 hours (Ref. 212). Most of the drug (approximately 85 percent of the dose) was recovered from the application site (i.e., was not absorbed). The remainder of the dose (approximately 15 percent) was detected in the blood within 1 hour after application, indicating that dermal exposure resulted in some systemic exposure. Maximum blood concentrations of isopropyl alcohol were attained at 4 hours and decreased steadily following removal of the test material. The half-life of elimination (T1⁄2) of isopropyl alcohol from blood was 0.77 and 0.94 hours for male and female rats, respectively. AUC was not determined. *(Proposed Rule, page 25191, FDA 2015)*

Further, in the Proposed Rule, the Agency concluded the following based on the studies that it reviewed and in the absence of the AUC for IPA from the Boatman et al study:

> While these data are adequate to define the ADME profile of isopropyl alcohol following non-dermal exposure, they are not sufficient to characterize what would occur following dermal exposure. Absorption data following dermal absorption in animals are still needed in order to

> determine the extent of systemic exposure following maximal dermal exposure to isopropanol-containing health care antiseptic products. Information on the distribution, metabolism, and excretion of isopropyl alcohol can be extrapolated from published data on the other routes of exposure. *(Proposed Rule, page 25191, FDA 2015)*

For FDA's review, the IPA Panel would like to provide the Agency with an estimate of the AUC based on the data available in Boatman et al. The Panel requests that the AUC estimate be discussed in a meeting with the FDA. The AUC estimate addresses the only limitation of this study provided by the Agency, which was conducted under good laboratory practice standards. The experimental design of the Boatman et al. study was also intended to provide a maximal dermal exposure to a 70% IPA concentrate as the exposure site was occluded and the exposure lasted 4 hours, which is equivalent to a continuous exposure lasting for more than half of a typical work day for a healthcare worker who might use an IPA skin antiseptic at 70% concentration. Although the Proposed Rule references IPA antiseptic concentrations as high as 91.3%, the Panel is not aware of any product with a concentration of IPA greater than 70%.

In addition, the IPA Panel would like to provide FDA with the updated IPA PBPK model (validated with data from Slauter et al. 1994) as an alternative method for the evaluation of systemic dose of IPA in humans. The IPA PBPK model can be adjusted to account for the higher exposure requirements of a MUsT assay in order to predict potential human fate. The IPA Panel would like to discuss the model with FDA and the value of its use to determine human IPA pharmacokinetics.

**II. Discuss Additional Data Provided for Oral Carcinogenicity:**

In Table 9 of the Proposed Rule, the FDA lists the criteria that must be fulfilled specifically with regard to the carcinogenicity endpoint (ICH S1A, S1B, and S1C). These criteria include a minimum of one species oral and one species dermal study for topical products. According to Table 9, this data will be used to identify potential carcinogenic risk associated with systemic and dermal exposure (dermal being the most appropriate route of exposure for topical products) associated with the active ingredient in the topical product, taking into consideration the type of toxicity, the level of exposure that produces these toxicities, and the highest level at which no adverse effects are expected to occur.

> ***Relevance of the oral carcinogenicity study*** – As noted by the FDA, IPA is primarily used in the clinical setting for dermal use (patient pre-operative skin preparations, healthcare personnel hand rub and surgical hand rubs). This use description is important as it helps to define the boundaries for the types of studies that are scientifically useful for evaluating potential adverse effects directly related to product end-use. According to

the ICH cancer guideline, (S1A), the "*route of exposure in animals should be the same as the intended clinical route when feasible*" (ICH, 1995). In addition, in the US FDA Redbook (Chapter IVC6; Section IVB), it is specified that the "*route of administration of the test substance should approximate that of normal human exposure, and if possible, the oral route should be used. A justification should be provided when using other routes*." (FDA, 2016)

Based on the use description, it is clear that the most appropriate routes of exposure for the chronic evaluation of IPA is dermal and inhalation (as a result of its high vapor pressure). IPA is not marketed for any use that should lead to oral ingestion. Unlike oral absorption, which is considered to be 100% of administered dose, systemic absorption of IPA following dermal exposure is considerably poor (Martinez et al, 1986). As an example, Boatman et al, (1998) reported that 84-86% of dermally administered IPA (70% solution) was recovered from the skin after 4 hours of exposure (occluded), suggesting <20% absorption. Based on the authors' calculations, <10% of administered dose was absorbed. This significant difference in absorption suggests that an oral carcinogenicity study in rodents would likely overestimate the potential for adverse effects with IPA exposure, compared to the dermal and inhalation routes which are most relevant to assessing actual human risk.

As noted above, the primary routes of human exposure to IPA is via dermal and inhalation. Aside from the over-estimation of systemic dose with oral exposure, available data indicates that the toxicokinetics of IPA differs based on the route of exposure. As shown in Slauter et al. (1994), the shape of the blood concentration curves for IPA following oral and intravenous (IV) (doses administered as bolus) exposures below saturable limits are similar. In both cases, peak blood concentration of IPA is reached within minutes of initial exposure and then falls with rapid elimination. In both cases, after the first hour following exposure, exposure is primarily to acetone as IPA is rapidly metabolized and/or eliminated from the blood (see Figures 3, 4 and 5 in Slauter et al, 1994).

With inhalation and dermal exposures, the blood kinetics of IPA is different than for IV and oral exposures. As shown in Figure 6 of Slauter et al. (1994), blood levels of IPA rise slowly over the 6-hour exposure period and then decline rapidly after exposures are terminated. Interestingly, blood kinetics with dermal exposure appears to be remarkably similar to that following inhalation exposure. As shown in Figures 1 and 2 below and Figures 2 and 3 in Boatman et al. (1998), blood IPA levels rose slowly without exceeding metabolic saturation over the exposure period and then declined following termination of exposures just as in the case of inhalation exposures below exposure levels that result in metabolic saturation.

Overall, based on the differences in blood kinetics, the IPA inhalation exposure study best mimics the potential blood kinetics that would be observed in a dermal IPA study compared to the bolus exposures expected with an oral study.

***Oral Carcinogenicity Study*** – In the FDA's response to Sponsor points proposed at the ACC-FDA meeting of October 20, 2015 (FDA, 2015b), the FDA provided its rationale for why it considered the existing 2-year inhalation toxicity study of IPA in the rat and mouse to be inadequate to fill the oral carcinogenicity data gap. The reasons provided by the FDA include:

- The study does not have adequate duration of weekly exposure of animals; and
- The study does not have adequate evaluation of target organ toxicity.

***(1) Study duration*** – While is it true that the exposure duration in the inhalation 2-year carcinogenicity test, proposed as an alternative to the oral carcinogenicity study (Burleigh-Flayer et al, 1997), was 5 days/week in contrast with the 7 days/week required in the FDA Redbook (Chapter IVC6; Section IVA), weight of evidence based on existing data demonstrates that the 5-7 day difference does not have a significant impact on toxicity as long as the same dose is maintained throughout the study duration. As an example, Slauter et al, (1994) conducted a toxicokinetic study to determine the impact of repeated exposures on the kinetics of IPA in rats. In the study, rats were either administered a single 300 mg/kg oral dose of IPA or repeated 300 mg/kg oral doses of IPA, once daily for 8 consecutive days. As a note, this relationship holds true only when the administered dose is below metabolic. As shown in Tables 5 & 6 of Slauter et al. (1994), metabolic rate (as determined by percent excretion of metabolites), elimination rate constants, half-life and AUC values for IPA were identical regardless of whether the same dose of IPA was administered once or on 8 consecutive days. In addition, the authors noted that greater than 80% of administered dose (below metabolic saturation) was eliminated within 24 hours of dosing. In essence, at doses/concentrations below metabolic saturation, a potential adverse systemic effect of exposure to IPA is likely to be related to peak exposures rather than cumulative exposures over time, since all administered IPA is essentially eliminated between exposures. Hence, peak systemic exposure in a 5-day exposure paradigm is expected to be identical to that in a 7-day exposure paradigm within the same dose group.

***(2) Target organ evaluation –*** To address this point, the observations and clinical tests required for the endpoint toxicity evaluation in a carcinogenicity test, set forth in the US FDA Redbook (Chapter IVC6; Section IVV), are provided in tabular form. Observations and clinical tests conducted in the rat and mouse inhalation carcinogenicity study are also provided for contrast in the table.

**Table 1:** comparison of endpoints/target organs evaluated in inhalation 2-year carcinogenicity studies of Isopropanol

| Observations and clinical tests | Required (US FDA Redbook) (FDA, 2007) | Rats (Burleigh-Flayer et al. (1997)) |
|---|---|---|
| Cage-side observations | Duration – once or twice daily | Duration – twice daily |
| | Signs – departure from normal activity, morbidity, mortality, gross observations for visible tumors | Signs – overt clinical signs, mortality, assessment for abnormal behavior/clinical signs, gentle palpation of internal organs |
| Body weights | Recorded weekly for first 13 weeks and monthly thereafter | Recorded for the first 14 weeks and every other week thereafter |
| Feed consumption | Measured at same interval as body weights | *** Food and water consumption data were reported in the 13-week study in rats and mice. No changes were found at identical concentrations (Burleigh-Flayer et al, 1994)** |
| Ophthalmological examination | To be performed on all animals before study begins and at the end of the study | Eyes of all rats examined prior to first exposure and during study week 71, 80, 104 (males) and 107 (females) |
| Hematology | Parameters – hematocrit, hemoglobin concentration, erythrocyte count, total and differential leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count, measure of clotting potential. *Reticulocyte counts and bone marrow cytology, as needed.* | Parameters measured – hematocrit, hemoglobin, erythrocyte count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total leukocyte count, differential leukocyte count, and platelet count. |
| Clinical chemistry | ALT, AST, SDH, GDH, TBA, AP, total bilirubin, GGT, 5'-NT, albumin, calcium, chloride, total cholesterol, cholinesterase, creatinine, globulin, glucose, phosphorus, potassium, total protein, sodium, triglycerides, urea nitrogen | **Glucose, ALT, calcium, urea nitrogen, AST, phosphorus, creatinine, GGT, sodium, total protein, potassium, albumin, chloride, globulin and total, conjugated and unconjugated bilirubin** |
| Urinalysis | Urine volume, specific gravity, pH, glucose, protein and evaluation for sediment and presence of blood/blood cells | Protein, glucose, renal epithelial cells, urine volume, osmolality. |
| Organ weights | Adrenals, brain, epididymis, heart, kidneys, liver, spleen, testes, thyroid/parathyroid, thymus, ovaries and uterus | Liver, kidneys, brain, heart, lungs, testes and spleen |

Note also that with the exception of the Harderian gland and Fallopian tubes, all other organs, as required in the US FDA Redbook, were microscopically examined (Burleigh-Flayer et al, 1997). As noted in Table 1, food consumption and clinical chemistry parameters were not performed in the 2-year carcinogenicity study. However, these endpoints were evaluated in the prior 13-week subchronic toxicity study of IPA at the same concentrations and no toxicologically-relevant changes were observed. No adverse effects to the liver were observed in either rodent specie at the end of the 2-year carcinogenicity study that could have been predicted by the clinical chemistry data. Overall, it is concluded that the chronic inhalation toxicity studies evaluated all endpoints that would have been required in an oral toxicity study. The IPA Panel would like to provide FDA with data from the Panel's sponsored 2 -year inhalation study for discussion at a meeting.

**III. Discuss Additional Data Provided for Dermal Carcinogenicity:**

As stated in Appendix B7 (Page 58), neither of the available subcutaneous or dermal bioassays were considered adequate by FDA for assessing the dermal carcinogenicity potential of IPA by the dermal route (FDA, 2014). IPA has not shown genotoxicity in multiple assays and has not shown effects that are consistent with a possible non-genotoxic mechanism of action for carcinogenicity. The primary metabolite of IPA, acetone, is routinely used by the National Toxicology Program (NTP) as a vehicle for dermal carcinogenicity studies without evidence of carcinogenicity due to repeated application. Thus, there is no evidence to support IPA metabolism to a carcinogenic substance on skin application.

In evaluating the carcinogenicity of IPA upon dermal exposure, two issues should be addressed:

- Potential for systemic tumors following dermal penetration of IPA; and
- Potential for skin cancer.

***(1) Systemic* effects** – Although there is no dermal 2-year carcinogenicity study available in rodents, the potential for systemic neoplasms with dermal exposure to IPA can be evaluated based on inhalation carcinogenicity data in rats and mice (Burleigh-Flayer et al, 1997). Since the potential for systemic effects is directly related to systemic dose, existing PBPK model for IPA was used to predict the time-course for venous blood concentration and AUC for IPA in rats (following dermal exposure) and comparing it to identical parameters in rats exposed to IPA via inhalation (Clewell et al, 2001). Model parameters for both studies are indicated below:

**Inhalation study –** The inhalation study modeled a 500 ppm 6-hour/day IPA exposure to rats. Based on the short half-life for IPA, the AUC and elimination rates for IPA are identical

whether exposures occur as a single dose or as repeated exposures. Hence, a single exposure scenario was modeled. The 500 ppm concentration was selected as this has been shown to be considerably below saturable concentration in rodents (Slauter et al, 1994) and was the lowest concentration tested in the existing inhalation carcinogenicity study (Burleigh-Flayer et al, 1997).

**Dermal study –** The dermal study modeled a 1500 mg/kg (equivalent to 0.42 ml, assuming average rat body weight of 220 g) administered dose in rats. The 1500 mg/kg dose was selected since it is higher than the 1000 mg/kg oral limit dose for carcinogenicity studies under the OECD test guidelines (OECD, 1994). In the model, exposure was considered to occur for 6 hours under occlusive conditions. Surface area for exposure was estimated to be 4.3 cm2 (Boatman et al, 1998; Slauter et al, 1994) to a 100% neat solution of IPA. Other model parameters included absorption rate for IPA (0.85 ± 0.04 mg/cm2/hr) and permeability constant (Kp) of 1.5 x 10-3 cm/hr, calculated in Boatman et al. (1998).

Results of the time-course for venous blood concentrations in both models are presented in Figures 1 and 2 below:

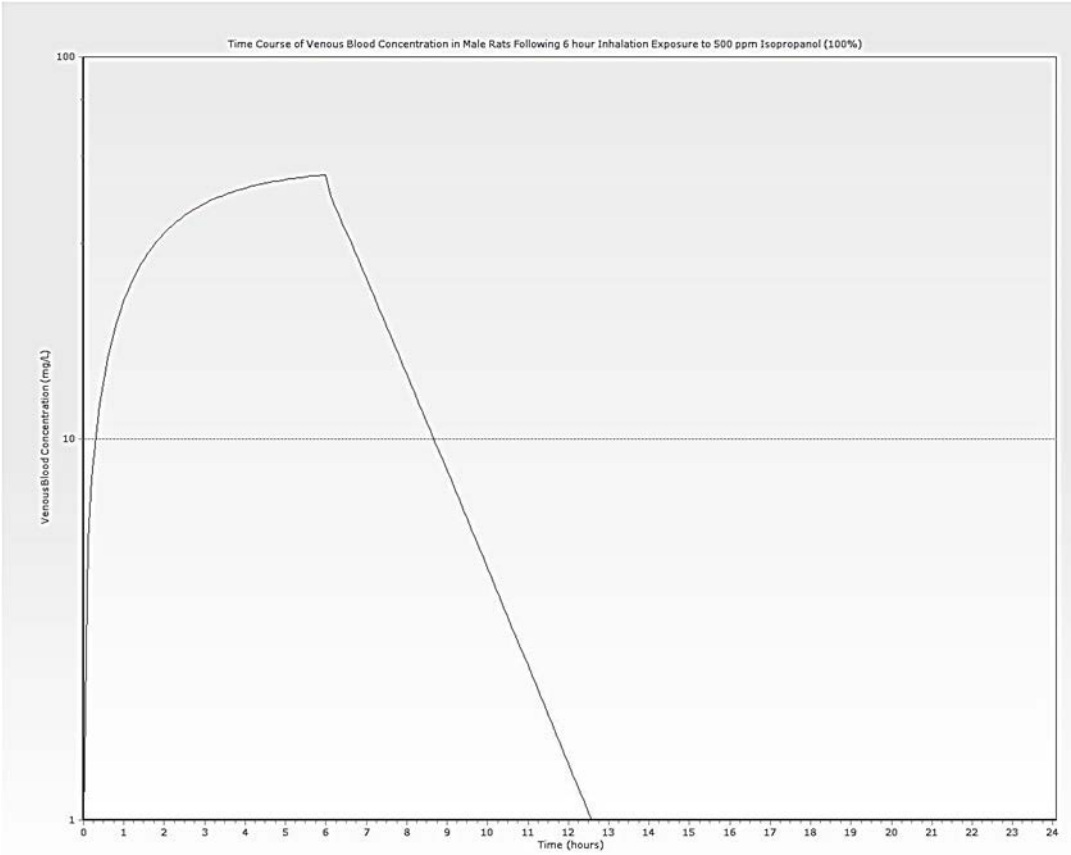



**Figure 1:** Time-course for venous blood concentration in male F-344 rats following 6 hour inhalation exposure to 500 ppm IPA. (Modeled results; Clewell, 2001)

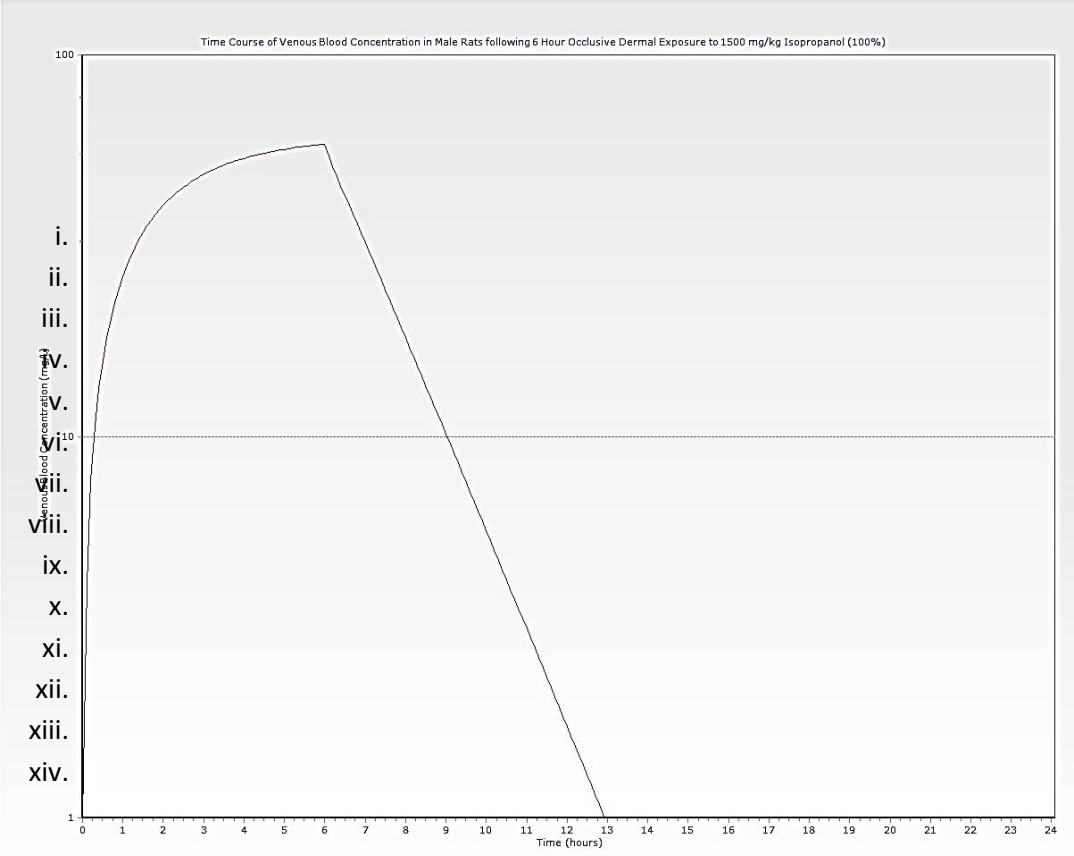



**Figure 2:** Time-course for venous blood concentration in male F-344 rats following 6 hour occlusive dermal exposure to 1500 mg/kg IPA. (Modeled results; Clewell, 2001)

As shown in Figures 1 and 2 above, the time-course for venous blood concentration for a male rat exposure to 500 ppm IPA for 6 hours is practically identical to that for a male rat exposed to 1500 mg/kg IPA through the skin for 6 hours under occlusive conditions. Based on the PBPK model, AUC for the inhalation study was predicted to be ~305 mg.hr/L while the AUC for the dermal study was predicted to be ~357 mg.hr/L. These values are consistent with the modeled simulations of inhalation data in rats (AUC at 500 ppm was ~ <500 mg.hr/L) shown in Figure 7c of Clewell et al. (2001). To further validate the models, the modeled data in Figure 1 (rat inhalation exposure to 500 ppm IPA) was compared to average blood concentrations of IPA in blood of male/female rats exposed (nose-only) to 500 ppm IPA for 6 hours (see Figure 6 of Slauter et al, 1994). The shape of the blood concentration curve from the in vivo data was identical to the modeled data, with IPA cleared from the blood within 12-13 hours, as shown in Figure 1.

In essence, data from Figures 1 and 2 indicate that the systemic dose in rats exposed to 500 ppm IPA in a 2-year carcinogenicity study is likely to be identical to that obtained if the rats

were dermally administered 1500 mg/kg bw/day of 100% IPA for 2 years. Based on the absence of effects in the inhalation study, an equivalent dermal carcinogenicity study would yield no evidence for systemic toxicity or carcinogenicity.

It should be noted that the low systemic dose of IPA in the dermal model is consistent with data from Boatman et al. (1998) showing poor dermal absorption of administered IPA through the skin in rats. In the Boatman et al. study, the authors calculated an absorption rate of 0.85 mg/cm2/hr (3.66 mg IPA/hr) in males. This translates to approximately 14.64 mg IPA absorbed over a 4-hour period under occlusive conditions. Based on a dermally applied dose of 0.18 g IPA in male rats with average body weight of 220 g, total absorbed dose over the 4 hr exposure period is equivalent to approximately 8% of administered dose . Since the study was conducted under occlusive conditions, the authors speculated that absorbed doses would be predictably less under typical human exposure conditions where exposure conditions are without occlusion.

***(2)*** **Potential for skin cancer –** Epidemiological evidence exists to indicate that IPA does not cause skin cancer in humans. The IARC 1999 monograph on IPA cites a case-control study that estimated the association between 293 workplace substances and several types of cancer, with 4% of study subjects exposed to IPA. The study authors concluded that there was no indication of an excess risk of skin melanoma due to isopropanol (Siemiatycki, 1991 reviewed in IARC, 1999). Tables 2.1 and 2.2 in IARC, 2012 lists nine cohort studies and two case-control studies of workers occupationally exposed to IPA manufactured through the strong-acid process. Although IARC concluded that there was sufficient evidence in humans for cancer of the nasal cavity following exposure to IPA manufactured through the strong-acid process, none of the studies indicated any evidence for excess risk to skin cancer.

The US National Institute for Occupational Safety and Health (NIOSH) published criteria for a recommended standard for occupational exposure to IPA (NIOSH, 1976). This report included a review of four epidemiological studies of occupational exposure to IPA (two of which were reviewed in the IARC report noted above). Consistent with the IARC report, the NIOSH report concluded that there was a carcinogenic hazard associated with the strong-acid process in IPA manufacture. None of the reports provided any evidence for cancer of the skin either as a result of the manufacturing process or exposure to IPA itself. Overall, the report concluded that “there is no evidence that isopropyl alcohol itself is a carcinogen”.

It is important to note that existing IPA studies (spanning varying production processes, occupational types and over a period of more than 50 years) have not provided a single case as evidence to suggest the potential for IPA to cause skin cancer. Considering that IPA has been used primarily in skin applications for over 90 years, it is instructive to also note that there is no case study suggesting evidence for skin cancer with IPA exposure. On this basis, it a dermal carcinogenicity study in rats or mice is not warranted.

The IPA Panel would like to provide and discuss with FDA the IPA PBPK model and additional skin histopathology data from the Panel's sponsored dermal carcinogenicity study.

**IV. Discuss Additional Data Provided on Hormonal Effects:**

In the Proposed Rule, the FDA notes that additional testing will be required for the purpose of assessing IPA's potential for hormonal/endocrine effects (FDA, 2015). Further research into the hormonal effects of IPA has been justified citing the study of Gorkal et al. that indicated dopamine, noradrenaline, and serotonin were either decreased or increase depending on the area of the brain studied (Gorkal, 1989). However, this is a non-guideline, high dose study, through a novel route of exposure, unrepeated, and without an apical endpoint associated with the observations. The authors note that methanol and ethanol can alter monoamine levels in the brain although the pattern of response is different. Therefore, the changes in neurotransmitters are indicative of a "class effect" notably of the narcotic action observed for small molecular weight alcohols and not a function of hormonal/endocrine imbalance per se.

During the October 20, 2015, meeting, IPA agreed to submit to the FDA a weight of evidence (WOE) on the hormonal effects of IPA. FDA staff also directed the Panel to current FDA guidance entitled, "Nonclinical Evaluation of Endocrine-Related Drug Toxicity: Guidance for Industry" on which to base our weight of evidence assessment. Nonclinical assessments include data from the following areas: 1) Receptor-Binding Assays; 2) Repeat Dose Studies; 3) Developmental and Reproductive Toxicity Studies; and 4) Carcinogenicity Studies.

In our review of the data, the IPA Panel found a lack of evidence for any endocrine related activity from *in vitro*, repeat dose, reproductive and developmental or carcinogenic studies. *In vitro* data was downloaded from the US EPA Toxcast system. This system provides high throughput testing data on estrogen and androgen receptor-mediated bioactivity and provides the information to assess and direct, via a weight of evidence approach, future endocrine activity testing. This approach is outlined in EPA's "Integrated Bioactivity and Exposure Ranking: A Computational Approach for the Prioritization and Screening of Chemicals in the Endocrine Disruptor Program." According to this paradigm, the weight of evidence does not support the contention that IPA has endocrine activity.

Subacute, subchronic and chronic repeat dose studies with IPA in rats and mice also fail to indicate that IPA has any target organ toxicity to male or female reproductive organs upon gross or microscopic examination of male or female reproductive organs. The only effect seen in grossly or histopathologically was testicular effects at doses that caused overall toxicity to the male or spurious increases in testicular weight that had no histopathologic correlate and were considered non-treatment related.

For the reproductive/developmental studies presented here, no adverse effects were seen at the highest dose tested or unless the levels were also maternally toxic. A more comprehensive review of reproductive and developmental studies was conducted by Faber et al 2008. A comparison of studies on the effects on males and mating ability indicated that the NOEL for IPA at this endpoint was at the guideline limit dose of 1000 mg/kg/day. When evaluating postnatal survival a NOEL was identified as 700 mg/kg/day.

The evidence presented supports the Panel's earlier assessment that well conducted repeat dose, developmental/reproductive studies and carcinogenicity studies have been conducted and that organ weights, gross, and microscopic observations of the endocrine system have failed to indicate any significant and consistent findings that IPA is hormonally active. Higher tiered multigenerational reproductive studies also do not provide any consistent and significant evidence that any apical endpoint of male and female index of reproductive function is affected at guideline limit dose or without significant confounding with maternal toxicity.

The IPA Panel would like to provide FDA with the Panel's WOE review and discuss further the results to determine whether additional endocrine testing is warranted for IPA.

**7. List of attendees invited by the sponsor for the Type C meeting to review data gaps for Isopropyl Alcohol.**

| Name | Title | Affiliation |
|---|---|---|
| Angela Lynch, MSPH, PhD | Isopropanol Panel Manager Toxicologist | American Chemistry Council |
| Komal Jain, JD | Isopropanol Panel Legal Counsel | American Chemistry Council |
| Brian Hughes, MPH, PhD, DABT | Toxicology Consultant | The Dow Chemical Company |
| David Adenuga, PhD | Senior Toxicologist | ExxonMobil |
| Satinder Sarang, PhD, DABT | Toxicologist | Shell International |
| Mike Ebers | Director of Regulatory Affairs | STERIS |
| John L. O'Donoghue, VMD, PhD, DABT | Consulting Toxicologist and Pathologist | STERIS |

**8. Requested FDA discipline areas and/or FDA staff to participate in the meeting.**

**a.** FDA staff with ADME and PBPK modeling expertise
**b.** FDA staff with carcinogenicity study expertise
**c.** FDA staff with hormonal effects expertise

**9. Suggested dates and times for the meeting.**

May 11, 13, 20, or 26 2016, morning or afternoon

**10. Meeting Format.**

The Isopropanol Panel requests a face-to-face meeting with FDA.

**11. References.**

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