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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Act. 412 REPOSPRESRECU Folios: 37

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Re: PI.-**BIOSYNTHIS.**-Solicitud de Patente de Invención en Fase Nacional PCT para **"COMPOSICIÓN OLEOSA VOLÁTIL ALTERNATIVA PARA SUSTITUIR CICLOMETICONAS EN FORMULACIONES COSMÉTICAS".**- Clase **C08L 91/06**.-Expediente número **11-151.129.**-

Yo, **ALICIA LLOREDA RICAURTE**, mayor, vecina de esta ciudad, identificada con la cédula de ciudadanía número 39.690.713 de Usaquén, Representante Legal en Bogotá para todos los asuntos relacionados con la Propiedad Industrial de la sociedad **BIOSYNTHIS**, organizada y existente de conformidad con las leyes de Francia y domiciliada en Saint Cyr Sous Dourdan, Francia, atentamente manifiesto a usted que interpongo **Recurso de Reposición** contra la Resolución número **27279** dictada por el señor Superintendente de Industria y Comercio el 29 de Abril de 2014 y notificada por Edicto fijado el 6 de Mayo de 2014, por medio de la cual se niega el privilegio de patente solicitado para la invención contenida en el expediente de la referencia.

I. FUNDAMENTOS DE DERECHO

Como fundamento de mi recurso me permito manifestar ante ese Despacho que en la Resolución N° 21380 se establece que la solicitud de patente en cuestión ha sido negada debido a que:

"...una persona medianamente versada en la materia y conocedora de los conceptos divulgados en los documentos D1 y D2, sin ningún esfuerzo modificaría las composiciones mencionadas en dichos documentos, incluyendo la adición de parafinas C7 - C21 dentro de la mezcla de parafinas volátiles, para obtener de esta forma la composición propuesta en la presente solicitud, de manera obvia o evidente"

así como también que:

"...el objeto de la solicitud en estudio consiste en obtener composiciones cosméticas volátiles libres de ciclometicona por ser tóxicas, donde estas composiciones tienen buena aceptabilidad organoléptica; dado que el Estado de la Técnica menciona composiciones sin ciclometicona y donde la diferencia en la composición de parafinas no puede generar un efecto técnico diferente, por cuanto la evidencia de la presente invención consiste en un "screening" organoléptico, las composiciones de la invención no pueden generar resultados diferentes a los que pueden generar las composiciones presentes en D1 y D2, puesto que éstas composiciones son muy similares entre sí".

Sin embargo, tal y como me permito mostrar en el presente recurso, las composiciones reveladas en la solicitud de patente en cuestión de ninguna manera de ninguna manera resultan evidentes a partir de las enseñanzas del estado de la técnica anterior.

1. Presentación de solicitud divisional

(a) Inicialmente y de conformidad con el Artículo 36 de la Decisión Andina 486 de 2000, el Artículo 7 del Decreto 2591 de 13 de Diciembre de 2000 y el Artículo 11 de la Resolución número 00210 de 15 de Enero de 2001, me permito manifestar que **la presente solicitud de patente se ha dividido en dos solicitudes**, a saber:

(i) Una solicitud compuesta por **11** reivindicaciones cuyo sustento se analizará en el numeral 2 del presente recurso; y,

(ii) Una solicitud divisional que comprende **10** reivindicaciones sustentadas en el capítulo reivindicatorio presentado originalmente junto con la solicitud de patente número **11-151.129**.

(b) En conexión con lo anterior, a continuación especifico los documentos anexos al presente memorial y que se relacionan con cada una de las solicitudes resultantes del presente fraccionamiento:

(i) **Solicitud original**: **"COMPOSICIÓN OLEOSA VOLÁTIL ALTERNATIVA PARA SUSTITUIR CICLOMETICONAS EN FORMULACIONES COSMÉTICAS"**

- Recibo número 14-0061386, expedido por la Superintendencia de Industria y Comercio, que que acredita el pago de las modificaciones mencionadas;

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- Copia de las páginas **19** a **21** que corresponde al nuevo capítulo reivindicatorio compuesto por **11** reivindicaciones; y

- Recibo número 14-0012453, expedido por la Superintendencia de Industria y Comercio, que acredita el pago por la reivindicación **11**.

(ii) **Solicitud Divisional**: **"COMPOSICIÓN OLEOSA VOLÁTIL ALTERNATIVA PARA SUSTITUIR CICLOMETICONAS EN FORMULACIONES COSMÉTICAS"**.

- Recibo número 14-0012356, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de los derechos que causa el presente fraccionamiento;

- Nuevo resumen-Objeto y Finalidad de la Invención; (formato digital)

- Páginas 1 a 18 de la descripción, que corresponden al texto de la descripción de la solicitud de patente número **11-151.129** originalmente presentada; (formato digital)

- Páginas **19** a **20** que corresponden al nuevo capítulo reivindicatorio compuesto por **10** reivindicaciones que, como se comentó previamente, encuentran pleno sustento en la descripción de la presente invención; (formato digital)

- Extracto de la solicitud, en sus dos formas, que incluye el título que se encuentra de acuerdo con el objeto de la presente invención fraccionada y que incluye la reivindicación 1; (formato digital)

- Tarjeta de propietario; (formato digital)

- Copia del documento que acredita el traspaso de los derechos de la presente invención que los autores de dicho invento hacen a favor de mi representado; (formato digital)

- Copia del documento que acredita a la suscrita ALICIA LLOREDA y/o al doctor GUSTAVO TAMAYO, y/o a la doctor IGNACIO SANTAMARIA y/o a al doctor ENRIQUE ALVAREZ, en los términos del Párrafo 1º del Artículo 543 del Decreto-Ley 410 de 1971, como Representantes Legales en Bogotá para todos los asuntos relacionados con la Propiedad Industrial de la sociedad **BIOSYNTHIS,**

organizada y existente de conformidad con las leyes de Francia y domiciliada en Saint Cyr Sous Dourdan, Francia; (formato digital) y

- Formato Único de Conversión, División y Fusión de Solicitudes.

(c) Teniendo en cuenta que la fecha de presentación de la solicitud parental es **8 de Noviembre de 2011,** atentamente solicito a usted tener como fecha de presentación de la solicitud fraccionada la misma fecha antes mencionada, y asignar el número de expediente correspondiente.

(d) En cuanto a la reivindicación de la prioridad respecto de la solicitud divisional, es la misma invocada en la solicitud original, la cual fue reivindicada oportunamente en Fase Internacional de las solicitudes número FR 0952400 de 10 de Abril de 2009 y US 61/173,349 de 28 de Abril de 2009.

(e) Ratifico a usted que la sociedad titular de la solicitud fraccionada en cuestión es **BIOSYNTHIS**, organizada y existente de conformidad con las leyes de Francia y domiciliada en Saint Cyr Sous Dourdan, Francia.

(f) Así mismo, reitero a usted que el documento que acredita mi calidad de Representante Legal en dicha sociedad para todos los asuntos de la Propiedad Industrial, fue presentado junto con mi memorial de **27 de Marzo de 2012**.

(g) De conformidad con lo establecido por el Artículo 36 de la Decisión 486 de 2000, solicito a ese Despacho se sirva aceptar y estudiar la solicitud divisional presentada y conceder el privilegio de patente solicitado.

2. Modificaciones realizadas en el capítulo reivindicatorio de la solicitud parental

Inicialmente me permito señalar que el capítulo reivindicatorio ha sido modificado de la siguiente manera:

- En la reivindicación 1 se ha especificado que las parafinas lineales seleccionadas entre C_8, C_{10}, C_{12} y mezclas de las mismas, corresponden a parafinas lineales de origen vegetal; y,

- Se ha adicionado una nueva reivindicación, la cual corresponde a la nueva reivindicación 11 y está dirigida a proteger el proceso mediante el cual se obtienen las parafinas lineales que componen las composiciones reveladas por el solicitante. Dicha

nueva reivindicación encuentra pleno sustento en, por ejemplo, la página 4 de la descripción.

Visto lo anterior me permito manifestar que las modificaciones realizadas no amplían de manera alguna el alcance de protección de la solicitud originalmente presentada, cumpliendo por lo tanto a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 34 de la Decisión 486 de 2000.

3. <u>Las composiciones reveladas son inventivas frente a las enseñanzas del estado de la técnica anterior</u>

Ahora bien, con el ánimo de demostrar el inequívoco carácter inventivo de la materia revelada en la presente invención frente a las enseñanzas de los documentos D1 y D2 señalados por el señor Examinador, atentamente me permito presentar las siguientes consideraciones técnicas:

- **Las diferencias con D1 y D2 van más allá de la longitud de las parafinas empleadas**

De acuerdo con lo afirmado por ese Despacho en el segundo párrafo de la página 4 de la Resolución aquí impugnada:

> *"La diferencia entre las composiciones divulgadas en la presente solicitud con respecto a las definidas en los documentos D1 y D2, radica en que las composiciones de la solicitud contienen dentro de la mezcla de parafinas lineales una proporción de parafinas C_{14}-C_{24}, mientras que las mezclas de parafina divulgadas en los documentos D1 y D2, se limita a parafinas C_{10}-C_{13}"*

Con la anterior afirmación se desconoce por parte de ese Despacho que la principal diferencia entre la materia revelada en la presente invención y las enseñanzas de los documentos D1 y D2 es que entre el 50% y el 100% en peso de la composición revelada en la solicitud de patente en cuestión corresponde a una mezcla de parafinas lineales que consiste de: i) entre el 70% y el 99% en peso de una parafina lineal de origen vegetal seleccionada de las parafinas C_8, C_{10}, C_{12} y mezclas de las mismas; y ii) entre el 1% y el 30% en peso de una parafina lineal C_{14} a C_{24}.

En relación con lo anterior me permito señalar explícitamente que los alcanos que hacen parte de las composiciones reveladas en los documentos D1 y D2 de ninguna manera pueden corresponder a cadenas lineales con un número par de átomos de carbono como consecuencia de su proceso de obtención.

En efecto, los hidrocarburos empleados en D1 corresponden básicamente a una mezcla de undecano (C11) y tridecano (C13), los cuales son preparados a partir de una reacción de hidrogenación de alcoholes en presencia de un catalizador de níquel, por ejemplo:

$$\text{dodecanol} + 2H_2 \rightarrow \text{undecano} + H_2O + CH_4$$

donde resulta relevante destacar adicionalmente que uno de los productos de reacción es el gas metano, ampliamente conocido por generar un impacto cerca de 25 veces mayor que el dióxido de carbono sobre el efecto invernadero.

Adicionalmente, al pretender obtener dodecano a través de dicho proceso es claro que se requeriría partir de tridecanol, el cual es ampliamente conocido por ser un alcohol de origen sintético.

Contrario a lo anterior, las composiciones de la presente invención se caracterizan porque comprenden parafinas lineales con un número par de átomos de carbono, lo cual es el resultado de que son sintetizados mediante un proceso de deshidratación de alcoholes naturales plenamente descrito por el solicitante y que está conformado por los siguientes dos pasos (se emplea el dodecanol como reactivo de ejemplo):

1) Deshidratación de dodecanol (en la presencia de un catalizador ácido):

$$\text{dodecanol} \rightarrow \text{dodeceno} + H_2O$$

2) Hidrogenación del dodeceno para obtener dodecano:

$$\text{dodeceno} + H_2 \rightarrow \text{dodecano}$$

y donde el balance de la síntesis es el siguiente:

$$\text{dodecanol} + H_2 \rightarrow \text{dodecano} + H_2O$$

siendo claro que dicho proceso implica que el único co-producto de reacción es agua, más no metano.

En conclusión, es claro que la composición revelada se caracteriza porque comprende únicamente alcanos procedentes de alcoholes vegetales y que corresponde a cadenas lineales con un número par de átomos de carbono, característica que de ninguna manera puede encontrarse en las composiciones del documento D1 debido al método de síntesis empleado por los autores de dicha anterioridad (en este punto resulta de gran importancia destacar que los alcanos de origine vegetal corresponden

exclusivamente a cadenas lineales con número par de átomos de carbono, mientras que los alcanos procedentes de compuestos petroquímicos son mezclas de cadenas lineales con números pares e impares de átomos de carbono).

Lo anterior implica entonces que existen marcadas diferencias entre las composiciones bajo análisis, toda vez que los elementos que las componen no son los mismos, y de hecho presentan drásticas diferencias en sus propiedades físico-químicas (presión de vapor, entalpía de vaporización, punto de ebullición, entre otros) y sus perfiles toxicológicos, tal y como se analiza en detalle más adelante en el presente recurso.

Por su parte, el documento D2 divulga una composición cosmética, tal como rímel, que comprenden aceites volátiles tales como isoparafinas C11/C12, es decir, alcanos ramificados y siliconas cíclicas (Párr. 0009). Estos aceites volátiles pueden representar del 10 a 80%, preferiblemente del 25 a 50% de la composición cosmética, mientras que los aceites no volátiles representan del 1 a 30%, y preferiblemente del 5 a 15% de la composición cosmética. Dicha composición cosmética es una composición pastosa que tiene mayor durabilidad (Párr. 14 y 19 y Ejemplos).

Por lo tanto, el documento D2 no enseña o sugiere una composición oleosa volátil así como tampoco enseña la relación de aceites volátiles y no volátiles en una composición oleosa volátil tal y como se reclama en la presente solicitud.

- **Comparación del perfil toxicológico de los alcanos C11 y C13 en relación con los alcanos C12 y C14**

Durante los últimos diez años, la seguridad sanitaria lograda a partir de la materia prima empleada en la industria cosmética ha sido blanco de múltiples y estrictas regulaciones con el fin de evitar al máximo posible el uso de productos potencialmente carcinogénicos y mutagénicos.

En relación con lo anterior, resulta de gran importancia destacar que de acuerdo con estudios avalados por el Instituto nacional de Salud de los Estados Unidos (www.ntp.niehs.nih.gov/undecane_508.pdf → ANEXO II)), el undecano y el tridecano son compuestos químicos altamente sospechosos de presentar actividad carcinogénica.

Adicionalmente, a través de pruebas in vitro sobre células epidérmicas humanas se ha podido establecer que el undecano es un compuesto con una elevada actividad pro-inflamatoria (Allen et al., 2011), así como también es sospechoso de generar toxicidad sobre el sistema neurobiológico, así como de inducir efectos tóxicos en los riñones, el hígado y el sistema hematopoyético.

Finalmente, el Instituto Nacional de salud destaca el efecto inductor de carcinogénesis por parte del nonano (C9) y el tridecano (C13).

Ahora bien, contrario a lo anterior los alcanos cuya estructura incorpora un número par de átomos de carbono no son sospechosos de ser tóxicos o poner en riesgo la salud humana (Ver ANEXO III: United States Environmental Agency - Voluntary Children Chemical Evaluation Program: Data needs assessments of n-alkanes, April 2007).

Visto lo anterior, me permito manifestar ante ese Despacho que más allá de obtener composiciones alternativas a las ya conocidas en el estado de la técnica, el problema técnico abordado y efectivamente resuelto por el solicitante de la presente invención fue el de desarrollar composiciones cosméticas seguras a partir de alcanos obtenidos de fuentes vegetales.

- **Implicaciones ambientales de las composiciones reveladas en la presente invención**

Frente a la discusión de la química verde, -cuyos principios básicos han sido adoptados en su totalidad por la comunidad científica-, (ANEXO IV → K. Aken, et al., Eco-scale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters, Beilstein Journal of Organic Chemistry, 2006, 2:3, doi: 10.1186/1860-5397-2-3), los dos principales criterios en orden de importancia son conocidos como: i) 'la economía del átomo', y ii) 'el factor ambiental'.

Con respecto al primer factor (el cual es definido como la razón estequiométrica del peso molecular de la molécula de interés sobre la suma de los pesos moleculares de todos los productos de reacción), al comparar los procesos descritos en el documento D1 y la solicitud de patente en cuestión para la síntesis del undecano y el dodecano respectivamente, se obtienen los siguientes resultados:

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Proceso	Molécula de interés	Peso de la molécula de interés g/mol	Productos de reacción adicionales	Peso de los productos de reacción adicionales g/mol	Suma de la masa molar de los productos de reacción adicionales	Factor (%)
D1	undecano	178	H_2O, CH_4	18, 16	34	83,9
Invención	dodecano	186	H_2O	16	18	**91,1**

siendo claro que el proceso de síntesis revelado en la presente invención ofrece un factor de "economía de átomo" mayor que el factor logrado a través del proceso de síntesis divulgado en D1.

Ahora bien, con respecto al factor ambiental (el cual es definido como la cantidad de residuos generados por unidad de producto de interés producido), al comparar los procesos descritos en el documento D1 y la solicitud de patente en cuestión para la síntesis del undecano y el dodecano respectivamente, se obtienen los siguientes resultados:

Proceso	Molécula de interés	% de la molécula de interés *	Desechos líquidos (Kg)/ Molécula de interés (Kg)	Desechos gaseosos (Kg)/ Molécula de interés (Kg)	Factor Ambiental	Factor ambiental reducido a un número equivalente de átomos de carbono
D1 Ejemplo 1	undecano	63,9	0,11	0,19	0,30	0,027
Invención **	dodecano	99,1	0,08	0,09	**0,17**	**0,014**

**Porcentaje antes de la destilación y definido como el producto entre la selectividad del undecano (100% undecano/suma de los productos de reacción) y la conversión de dodecanol (100 x (100 - % dodecanol/100)*

*** El proceso implica la deshidratación de dodecanol en presencia de alumino en medio ácido, seguido por la hidrogenación del dodeceno hasta formar el dodecano. Conversión de dodecanol " 99,9%. Selectividad final del dodecano = 99,2%.*

De lo anterior es claro que el factor ambiental del proceso empleado en la solicitud de patente en cuestión es cerca de 50% más bajo que el mostrado en D1, a lo cual se suma la no formación de emisiones de gases generadores del efecto invernadero.

Visto lo anterior me permito manifestar ante ese Despacho que la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1, D2 o la combinación de los mismos, cumpliendo por lo tanto a cabalidad con los requisitos de patentabilidad establecidos en el Artículo 18 de la Decisión 486 de 2000.

II. CONCLUSIONES

Con base en los argumentos técnicos mostrados previamente, me permito manifestar ante ese Despacho que la materia revelada en la solicitud de patente en cuestión de ninguna manera resulta evidente para la persona medianamente versada en la materia a partir de las enseñanzas del estado de la técnica anterior.

En consecuencia y en aras de restablecer los derechos vulnerados al solicitante, atentamente solicito a ese Despacho considerar los argumentos expuestos anteriormente y revocar en su totalidad la Resolución No 27279.

III. ANEXOS

Anexo al presente recurso me permito presentar:

(i) Copia de los documentos mencionados en el literal 1 (b) (ii) del presente recurso;

(ii) Copia del documento: "Summary of data for chemical selection", Prepared for NCI by Technical Resources International, Inc;

(iii) Copia del documento: "United States Environmental Agency - Voluntary Children Chemical Evaluation Program: Data needs assessments of n-alkanes, April 2007; y

(iv) Copia del documento: "K. Aken, et al., Eco-scale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters, Beilstein Journal of Organic Chemistry, 2006, 2:3, doi: 10.1186/1860-5397-2-3".

IV. PODER

Finalmente me permito recordarle a este Despacho que el documento que acredita mi calidad de representante legal en Bogotá para asuntos relativos a la Propiedad Industrial de la sociedad peticionaria, fue presentado ante dicha entidad con mi memorial de 27 de marzo de 2012.

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V. DOMICILIO

Mi dirección es Calle 72 No. 5-83, Piso 6º, Bogotá D.C.

Del Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

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Industria y Comercio
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*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	651483755	10/06/2014	11.842.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICACIONES O N.CREACION CORRECCION A SOLICITUD EN TRAMITE / MODOFICA	128.000.00	128.000.00
				$128.000.00

SON: **CIENTO VEINTIOCHO MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

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REIVINDICACIONES

1. Composición oleosa volátil que comprende:

(a) Desde 50 hasta 100% en peso de una mezcla de parafinas lineales que consiste de:

(i) 70 a 99% en peso de una parafina lineal de origen vegetal y seleccionada de las parafinas C_8, C_{10}, C_{12} y mezclas de las mismas.

(ii) 1 a 30% en peso de una parafina lineal C_{14} a C_{24}, y

(b) Desde 0 hasta 50% en peso de un aceite no volátil seleccionado de hidrocarburos ramificados minerales o sintéticos, (poli)ésteres y (poli)éteres, (poli)ésteres de ácidos C_2–C_{24} y alcoholes C_2–C_{24} o polioles, que son ramificados, triglicéridos de ácidos grasos C_6–C_{20}, aceites vegetales, dialquilcarbonatos, ácidos grasos ramificados y/o insaturados, alcoholes grasos ramificados y/o insaturados, aceites de silicona, aceites de fluorosilicona, aceites fluorados, y mezclas de los mismos,

donde la composición oleosa tiene un punto de ignición por debajo de 100°C.

2. Composición de acuerdo con la reivindicación 1, caracterizada por que comprende 90 a 99% en peso de parafina(s) C_8, C_{10}, C_{12} y de 1 a 10% en peso de parafina(s) C_{14} a C_{24}.

3. Composición de acuerdo con la reivindicación 2, caracterizado en que comprende o consiste sólo de, dodecano y tetradecano.

4. Composición de acuerdo con cualquiera de las reivindicaciones 1 a 3, caracterizada porque contiene 70 a 95% en peso de una mezcla de parafina y 5 a 30% en peso de aceite(s) no volátil(es).

5. Composición de acuerdo con cualquiera de las reivindicaciones 1 a 3 caracterizada porque contiene 85 a 95% en peso de mezcla de parafinas y 5 a 15% en peso de aceite(s) no volátil(es).

6. Método o proceso para mejorar el uso de rímel, lápiz labial o base, de polímeros de silicona tales como elastómeros de silicona o gomas, o para mejorar el esparcimiento en la piel de composiciones de protección solar y/o la dispersión de pigmentos en composiciones de protección solar añadiendo al rímel, lápiz labial, fundación, polímeros de silicona, gomas o composiciones de filtro solar la composición oleosa de acuerdo con cualquiera de las reivindicaciones 1 a 5.

7. Composición cosmética que contiene la composición oleosa de acuerdo con cualquiera de las reivindicaciones 1 a 5.

8. Composición de acuerdo con la reivindicación 7, caracterizada porque no contiene siliconas cíclicas.

9. Método o proceso para maquillaje y/o cuidado y/o protección de la piel, labios, pestañas, y/o uñas aplicando sobre la piel, labios, pestañas, y/o uñas la composición cosmética de acuerdo con cualquiera de las reivindicaciones 7 y 8.

10. Método o proceso para mejorar la evaporación y/o aplicación en la piel de composiciones antitranspirantes o desodorantes, particularmente en forma de roll-on, gel o barra, particularmente basadas en sales de aluminio añadiendo a composiciones antitranspirantes o desodorantes la composición cosmética de acuerdo con cualquiera de las reivindicaciones 7 y 8.

11. Una composición oleosa volátil que comprende:

    a) Desde 50 hasta 100% en peso de una mezcla de parafinas lineales que consiste de:

    (i) 70 a 99% en peso de una parafina lineal de origen vegetal y seleccionada de las parafinas C_8, C_{10}, C_{12} y mezclas de las mismas.

    (ii) 1 a 30% en peso de una parafina lineal C_{14} a C_{24}, y

b) Desde 0 hasta 50% en peso de un aceite no volátil seleccionado de hidrocarburos ramificados minerales o sintéticos, (poli)ésteres y (poli)éteres, (poli)ésteres de ácidos C_2–C_{24} y alcoholes C_2–C_{24} o polioles, que son ramificados, triglicéridos de ácidos grasos C_6–C_{20}, aceites vegetales, dialquilcarbonatos, ácidos grasos ramificados y/o insaturados, alcoholes grasos ramificados y/o insaturados, aceites de silicona, aceites de fluorosilicona, aceites fluorados, y mezclas de los mismos,

donde dicha composición oleosa tiene un punto de ignición por debajo de 100°C,

y donde dicha composición se caracteriza porque la mezcla de parafinas lineales de origen vegetal es obtenida mediante un método que comprende las siguientes etapas sucesivas:

- Deshidratación de al menos un alcohol graso C_8-C_{24} para obtener un alqueno; y,
- Hidrogenación de dicho alqueno para obtener un alcano.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0012453

Bogotá D.C., Febrero 03 de 2014 - 16:59:00

RECIBIDO DE : LLOREDA & CIA. S.A. NI 830.022.145 RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
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RECIBO DE CA	999999999	134861	26/12/2013		505.000.00
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RECIBO DE CA	999999999	134863	26/12/2013		505.000.00
RECIBO DE CA	999999999	134864	26/12/2013		505.000.00
RECIBO DE CA	999999999	134865	26/12/2013		505.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	31.000.00	31.000.00
				$31.000.00

SON: **TREINTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-*****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-151129- -00010-0000

Fecha: 2014-06-13 17:01:15 Dep. 2020 DIR.NUEVASCR
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SUMMARY OF DATA FOR CHEMICAL SELECTION

Undecane
1120-21-4

BASIS OF NOMINATION TO THE NTP

Undecane is brought to the attention of the Chemical Selection Working Group as an environmental pollutant with widespread human exposure but limited toxicological information.

Undecane was selected from a group of hydrocarbons found in fuels and solvents, but it is also a ubiquitous air pollutant in outdoor and indoor environments, and in water. The National Institute for Occupational Safety and Health (NIOSH) estimated that approximately 1,129 workers are exposed to undecane based on a 1980s survey. However, its main uses as a solvent and as a component of diesel fuels and kerosene do not appear to be reflected in the NIOSH survey.

No adequate 2-year carcinogenicity study of undecane was found in the available literature. Undecane was a tumor promoter in the classical skin tumor promotion model using benzo[a]pyrene as the initiator. In *in vitro* studies, undecane was not mutagenic in *Salmonella typhimurium*.

Undecane may have a considerable human toxicological impact since it is found in many situations where proven carcinogenic hydrocarbons such as fuel combustion products or cigarette smoke are also present.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

According to the NTP reviewers of the summary sheets on decane and undecane, a draft report (TR-519) of a 2-year carcinogenicity study of Stoddard solvent is tentatively scheduled for peer review in May 2003. Male Fischer 344 rats inhaled Stoddard solvent at doses of 0, 188, 550, or 1100 mg/m^3 and female Fischer 344 rats and male and female B6C3F$_1$ mice were exposed at 0, 550, 1100, or 2200 mg/m^3. Stoddard solvent is a widely used chemical mixture, with production in 1990 exceeding 38 million pounds. Stoddard solvent contains hydrocarbons ranging from C7 to C12, with the majority in the C9 to C11 range. The hydrocarbons are 30-50% alkanes, 30-

Prepared for NCI by Technical Resources International, Inc. to support chemical nomination under contract no. NO2-CB-07007 (11/02, 3/03)

40% cycloalkanes, and 10-20% aromatics. Both decane and undecane are present in Stoddard Solvent. Although Stoddard solvent was negative in the micronucleus assay, pathologic studies on the mice have been completed. These studies indicate treatment-related effects in the liver in both sexes of mice. The pathologic results in the rats were not available for the CSWG's evaluation.

SELECTION STATUS: Selected

ACTION BY CSWG: 12/17/02

Studies Requested:

Carcinogenicity

Priority: High

Rationale/Remarks:

- Consider nomination with decane and select one of these chemicals for testing.
- Consider also testing in an initiation/promotion protocol.
- Test pure compound rather than a complex mixture of alkanes.
- Ubiquitous air pollutant with widespread human exposure.
- Some evidence that this class of chemicals act as tumor promoters.
- HPV chemical; industry is sponsoring a mixture of alkanes

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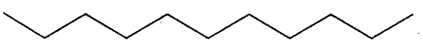
CHEMICAL IDENTIFICATION

CAS Registry No.:1120-21-4

Synonyms:Hendecane, *n*-undecane, alkane C_{11} (ChemID, 2002; Lide, 2000; Sigma-Aldrich, 2002a)

Structure, Molecular Formula, and Molecular Weight:



$C_{11}H_{24}$ Mol. wt: 156.31

Structural Class: Aliphatic alkane

Chemical and Physical Properties:

Description:	Colorless liquid (Lewis, 2002; Verschueren, 2001)
Melting Point:	25.5 °C (Lide, 2002)
Boiling Point:	195.9 °C (Lide, 2002)
Flash Point:	65 °C (Lewis, 2002)
Solubility:	Sol. in ethyl alcohol and ethyl ether, insol. in water (Lide, 2002)
Density:	0.74 g/mL at 20 °C (Lide, 2002)
Reactivity:	Combustible (NTP, 2001); combustion products include CO and CO_2; incompatible with bases, oxidizing agents, and reducing agents (Sigma-Aldrich, 2002b)

Technical Products and Impurities: Undecane (≥99.8%, 99%, 99+%, or ≥97.0%) is available from Sigma-Aldrich (Sigma-Aldrich, 2002a).

EXPOSURE INFORMATION

Production and Producers:

Manufacturing Processes: Petroleum is the most abundant source of saturated hydrocarbons. Petroleum is separated into individual fractions by distillation in a refinery; these fractions can be processed further to obtain many organic chemicals. N-Alkanes having more than six carbons, such as undecane, are not fractionated individually but as mixtures of several homologues. These mixtures are isolated in high isomeric purity from higher boiling petroleum, gas-oil, and wax distillate fractions by selective separation techniques, such as molecular sieve separation or urea extractive crystallization (Griesbaum *et al.*, 1989; HSDB, 2002).

Before natural gas and petroleum became essential raw materials for organic chemicals, the most important source of saturated hydrocarbons was coal. Coal liquefaction provided the greatest variety of saturated hydrocarbons, the Fischer-Tropsch synthesis producing alkanes in the range of C_1 to C_{30} or higher (Griesbaum *et al.*, 1989).

Production/Import Level: Undecane is listed in the US Environmental Protection Agency's (EPA's) Toxic Substances Control Act (TSCA) Inventory (ChemID, 2002).

Undecane is a high production volume (HPV) chemical with production exceeding 1 million pounds annually in the US. It has no sponsor in the HPV Challenge Program (EPA, 2002).

Producers and Importers: According to Chemical Sources International, there are 18 US suppliers of undecane (Chemical Sources International, 2002).

Undecane is currently manufactured or distributed by Alfa Aesar/Johnson Matthey; Dow Chemical Company; Roper Thermals; and Spectrum Chemical Manufacturing Corporation (Chemcyclopedia, 2002; Hunter, 2002; Tilton, 2001).

Use Pattern: Undecane is a constituent of diesel oil and kerosene (Verschueren, 2001). Major uses include:

- jet-fuel and petroleum research
- distillation chaser
- chemical intermediate in the manufacture of chlorinated paraffins, linear alkylbenzenes, primary detergent alcohols, C_{11}-C_{14} paraffins, olefins, and sulfonates
- feedstock for citric acid production by fermentation
- solvent, especially for printing inks and degreasing applications (HSDB, 2002; Lewis, 2002).

Undecane was listed as a synthetic flavoring agent in a Japanese report (Yoo, 1986).

Undecane is also found in several widely used petroleum distillates, such as Stoddard solvent and jet fuel. Undecane represents 2.7-17.5 % of white spirits, a mixture of saturated aliphatic and alicyclic, and alkyl aromatic C_7-C_{12} hydrocarbons. Stoddard solvent, a form of white spirit, is a mixture containing 30-50% linear and branched alkanes (ATSDR, 1995a; World Health Organization, 1996). The source used to prepare JP-4 jet fuel apparently affects the amount of decane present. Undecane was found at a percentage of 16.62 or 4.17 in JP-4 fuel when the source was shale or petroleum, respectively (Irwin, 1997).

In 1985, the US consumption of aliphatic hydrocarbon-based solvents in the paint industry was 433,000 tons. The annual sale of white spirits in the US was 717,000 tons in 1985 (World Health Organization, 1996).

Human Exposure:

Occupational Exposure: The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 1,129 workers in 51 facilities were potentially exposed to undecane in the workplace (Sigma-Aldrich, 2002). The NOES database does not contain information on the frequency, level, or duration of exposure to

workers of any chemical listed therein. Apparently the NOES survey does not address the presence of undecane in other solvents since NOES estimates, for example, that 1,922,235 employees in 142,653 facilities are exposed to Stoddard solvent (RTECS, 2000).

Exposure to undecane has been documented in a wide variety of occupational settings.

In a 1996 report, the possibility that the exposure of office workers to 0.3 ppb of undecane was associated with the use of carbonless copy paper was raised (NIOSH, 2000). Undecane was released from an idle photocopy machine and from a printing photocopy machine at a rate of 36 and 2,000 µg/hour (HSDB, 2002).

Undecane concentrations in the vulcanization area of a shoe-sole factory ranged from 1-170 $\mu g/m^3$. The observed undecane levels were probably due to the use of raw materials, curing temperatures, and high production rates (Cocheo *et al.*, 1983).

Workers employed in drilling operations that use low-aromatic oil-based drilling fluids may be exposed to undecane as these oils contain aliphatic hydrocarbons in the range of C_9-C_{15} (Eide, 1990).

Individuals working with jet fuel used in commercial or military aircrafts may be exposed to undecane since it is a prevalent component of these kerosene-based fuels (Riviere *et al.*, 1999).

Undecane was detected in gas samples emitted during the germination phase in malting and beer manufacture using a pilot-scale brewery (Gibson *et al.*, 1995).

Environmental Exposure: The general population is exposed to undecane via inhalation of ambient air, ingestion of food and drinking water, and dermal contact with products containing undecane (HSDB, 2002).

Undecane was detected in the breast milk of 7 of 12 samples from mothers living in four US urban areas. It was also identified in the breath and personal air samples collected from 50 individuals living in Los Angeles, California (HSDB, 2002).

Consumer Exposure: Undecane is found in pesticides, waxes and cleansers, building materials, adhesives, and paints used by consumers (Wallace *et al.*, 1985).

Undecane was detected in the interior of new cars as a component of volatile organic compounds (VOCs). A car that was on the market for 3 weeks had undecane concentrations of 870 $\mu g/m^3$. After 9 weeks, undecane levels decreased to 310 $\mu g/m^3$. VOC concentrations in new car interiors decreased approximately 20% per week (Brown & Cheng, 2000).

Dry cleaning solvents that remain on clothing are a source of undecane exposure. The total amount of undecane that evaporated from a pair of trousers was 1.09 mg in 5 days after dry cleaning. The undecane level on the fifth day was 32% of the first day's concentration and it was determined that the half time of undecane on this article of clothing was 2.7 days (Tashiro *et al.*, 1999).

Undecane was identified as a volatile component of peanut oil (heated between 150 and 200 °C), cheese, fried bacon, fried chicken, and raw beef (HSDB, 2002). It was also detected in coupons from food packages, contributing an off-flavor to foods such as breakfast cereals (Reineccius, 1991).

Undecane was detected in extracts of the plant species *Hypericum perforatum* (St. Johns wort) (European Commission, 2002), a popular dietary supplement used to treat mild to moderate depression.

The general population is also exposed to undecane through the inhalation of vapors from paints and lacquers containing white spirits (World Health Organization, 1996).

Environmental Occurrence: Undecane is found in crude oil, a naturally occurring substance found trapped among sedimentary rocks below the earth's surface (Chevron, 2002; NETLAB, 1997).

Air Pollution: Undecane has been detected among VOCs in several studies analyzing indoor air quality.

- Undecane was one of the most frequently reported chemicals in indoor air as mentioned in a review of the literature from 1979 to 1990 (Samfield, 1992).
- An EPA study of seven volunteers who performed 25 common activities found that painting and removing paint for 4 hours resulted in exposure to undecane at a concentration of 150 $\mu g/m^3$. A home where paint, solvents, paint thinners, kerosene, gasoline, and pesticides were stored had undecane levels as high as 290 $\mu g/m^3$ (Wallace *et al.*, 1989).
- In a Finnish study, the concentrations of 48 VOCs, including undecane, exceeded normal levels more often in sick houses than in normal houses. Sick houses were defined as dwellings in which inhabitants show symptoms such as headache, nausea, irritation of the eyes, and general malaise, among others (Kostiainen, 1995).
- Indoor concentrations of *n*-alkanes (C_8-C_{11}) and other organic solvents were significantly elevated in newly painted Swedish dwellings. *n*-Alkanes were emitted from both solvent- and water-based paints, the emissions being 100 times higher with solvent-based paints (Wieslander *et al.*,1997).
- Undecane was identified in 2 of 7 samples of household waste headspace at a concentration of 0.1-1 mg/m^3 in a Danish study (Wilkins, 1994).
- Undecane was detected in smoking and nonsmoking households or workplaces. The highest concentration of undecane, found in workplaces that allowed smoking, was a maximum value of 155 $\mu g/m^3$ (Heavner *et al.*, 1996).
- Indoor samples taken from 49 Columbus, Ohio homes in 1991 showed an average concentration of undecane in nonsmoking and smoking households of 3.86 and 14.5 $\mu g/m^3$, respectively (HSDB, 2002).
- Undecane concentrations ranged from 48.3 to 115.6 $\mu g/m^3$ in air samples collected in a new building during 1987-1988. A separate study reported concentrations of undecane between 5.5 and 14 $\mu g/m^3$ during a 1987-1988 sampling period, 2 to 3 years after the facility opened (HSDB, 2002).

- According to a 1987 EPA report, glued carpets, wallpapers, and cleaning agents and pesticides emit undecane. The highest concentration measured was for painted sheetrock with a value of 228 µg/m^3 (Wallace *et al.*, 1987). Undecane has also been detected after carpet installation, during application of acrylic floor wax, and during renovation (Chang & Guo, 1992; Shields & Weschler, 1990; Tharr, 1996).

- The indoor concentration of undecane in Dutch homes, 3-9 μg/m^3 (1981-1983) was dependent on their construction date (pre-war-<6 yrs old). Outdoor air concentrations were 0.4 μg/m^3 (median) with a maximum of 3 μg/m^3 (Verscheuren, 2001).

- The mean annual undecane concentration inside British homes was 14 µg/m^3 (MRC Institute for Environment and Health, 2000).

- In a 1983-1984 Italian study, the indoor and outdoor mean concentration of undecane was 80 and <2 μg/m^3, respectively (Verscheuren, 2001).

Undecane has been measured in the atmosphere of several US and European cities. Undecane was detected in roadway air, airfield air, and aircraft air in concentrations of 0.242, 1.7, and 4.89 ppb, respectively. The mean concentration of undecane in the Caldecott Tunnel (San Francisco, California) was 2.43 ppb (HSDB, 2002).

Undecane emissions from gasoline- and diesel-fueled cars passing through the Tuscarora Mountain Tunnel on the Pennsylvania Turnpike were 0.58 mg/mi and 4.27 mg/mi, respectively (Gertler *et al.*, 2002). Undecane emissions from light-duty gasoline vehicles were calculated to be 428 tons per year in a 1994 study conducted in Washington State (Brady *et al.*, 1998).

Soil Accumulation: In a 1986 study, hydrocarbon characterization of soils containing spilled crude oil (>3 yr) showed the presence of *n*-alkanes, including undecane, in some soil samples. The abundance of *n*-alkanes decreased in contaminated soils because of biological transformation and volatilization (Saterbak *et al.*, 1998).

Water Pollution: Undecane was detected in groundwater at 0.22-0.70 µg/L according to a 1980 US study. It has also been identified in US drinking water and in water samples from European rivers, lakes, and marine coastal waters. The concentration of undecane in surface water at an offshore oil production operation in the Gulf of Mexico was 310

μg/L (HSDB, 2002).

Industrial wastewater generated from publicly owned treatment facilities contained undecane in concentrations from 10 to 15 ppb (HSDB, 2002).

Undecane was one of over 300 compounds detected in neutral extracts of 24-hr composite samples from petroleum refinery wastewaters in a 1978 study (Burks, 1982).

Biodegradation and Ecotoxicity: Undecane can be degraded by naturally occurring marine microorganisms within 20 days when present in diesel oil. Anaerobic biodegradation can occur under methanogenic conditions (Verscheuren, 2001).

The EC_{50} in methanogens was 0.61 mg/L (Verscheuren, 2001). Undecane also inhibited bacterial spore germination on certain growth media (Cavender, 1994).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of undecane. Undecane was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the specific association of exposure to undecane and cancer risk in humans were identified in the available literature.

An epidemiological study of chronic workplace exposure to white spirits reported an odds ratio >1 for prostate cancer, Hodgkin's lymphoma, and squamous cell carcinoma of the lung. In addition, several epidemiological studies have shown increased risks of respiratory, pancreatic, kidney, and lung cancer in workers exposed mostly to white spirits. None of the studies mentioned above demonstrated a causal association between cancer and exposure to white spirits (ATSDR, 1995a; World Health Organization, 1996). The role of undecane, if any, was not examined.

Undecane, in solutions as strong as 30%, produced no skin irritation in human subjects when applied for 24 hours (Criteria Group for Occupational Standards, 1983).

Animal Data:

Acute Studies: The LC_{50} for undecane is reported to be >442 ppm/8hr in rats (Sigma-Aldrich, 2002b).

Undecane (0.05 ml) produced only mild irritation in the rabbit skin irritation test (Criteria Group for Occupational Standards, 1983).

Chronic/Carcinogenicity Studies: No 2-year carcinogenicity studies of undecane were identified in the available literature.

Undecane was shown to have tumor promoting activity. In a 1976 study, undecane (25 mg) and benzo[a]pyrene (BP) (5 μg) applied to the skin of female ICR/Ha Swiss mice, 3/wk for 440 days, induced papillomas in 41 of 50 animals. BP alone induced tumors in 12 of 50 animals in the same time, while undecane alone did not produce tumors (Van Duuren & Goldschmidt, 1976).

Several studies that examined the potential carcinogenicity of JP-4 jet fuel have been conducted. No increase in the incidence of tumors was found in rats and mice one year after 8 months of inhalation exposure to JP-4 fuel. In a 1993 study, F344 rats exposed to JP-4 at 5,000 mg/m^3 for 12 months had an increase of interstitial cell tumors in the testis 12 months after the termination of the exposure. However, mice exposed to the same regimen did not show an increase in the incidence of neoplastic lesions. Dermal administration of JP-4 jet fuel (25 mg, 3/wk for 105 wk) increased the incidence of squamous cell carcinomas and fibrosarcomas in mice exposed to shale-derived JP-4 (50% incidence), and in animals exposed to petroleum-derived JP-4 (26% incidence) compared to the appropriate controls (2% and 0%, respectively) (ATSDR, 1995b). The relevance of these studies to undecane has not been determined.

Short-Term Tests: Undecane was not mutagenic when tested in *Salmonella typhimurium* strains TA98, TA100, UTH8413, and UTH8414 at concentrations up to 2,000 μg/plate. Mutagenicity was not enhanced by rodent liver S-9 (Connor *et al.*, 1985). Undecane was negative in the rec-assay with *Bacillus subtilis* strains M45 (rec$^-$) and H17 (rec$^+$) (Yoo, 1986).

Undecane did not induce *in vitro* transformation of Syrian hamster embryo cells or Balb/3T3 mouse embryo fibroblasts. Neither did it enhance co-transformation when added with BP in both cell systems. Undecane also had no effect on intercellular communication in a monolayer of Syrian hamster embryo cells (Atchison *et al.*, 1985).

Metabolism:

Absorption and Distribution: Inhaled undecane is rapidly distributed from the blood to different organs and tissues, especially those with high lipid content. The concentrations of undecane in the brains and blood of rats exposed at 100 ppm, 12 hr/day for 3 days were 47.7 and 13.7 μmol/kg (Eide, 1990).

Aliphatic Hydroxylation: This process involves insertion of oxygen into a C-H bond.

Cleavage of the C-H bond by hydrogen abstraction is the rate-limiting step. In the case of simple, straight chain hydrocarbons, such as undecane, aliphatic hydroxylation occurs at both the terminal methyl groups and the internal methylene groups (Parkison, 1996).

Undecane may also directly affect P-450 enzyme activity. Undecane caused reduced recovery of products of liver and lung 7-ethoxycoumarin deethylase and of lung benzo[*a*]pyrene hydroxylase activities in microsome preparations from Sprague-Dawley rats. However, it did not reduce NADPH formation and did not affect P-450 reductase activity when the enzyme was assayed with the substrate, cytochrome *c* (Rabovsky *et al.*, 1986).

Other Biological Effects:

Cellular Damage: In an *in vitro* study, undecane induced the production of interleukin 8, a proinflammatory cytokine, in normal human epidermal keratinocytes (NHEK) (Allen *et al.*, 2001).

Neurological Alterations from Products Containing Undecane: Undecane may be linked to the development of neurological impairment associated with acute exposure to a high level of JP-4 jet fuel (ATSDR, 1995b). Minor neurological effects (dizziness, changes in simple reaction time, and visual-motor coordination) have also been reported in humans from short-term exposure to Stoddard solvent. Similarly, minor neurobehavioral changes were seen in subjects exposed to other white spirits (World Health Organization, 1996). More severe neurological changes were described from chronic exposure to Stoddard solvent, white spirits, and other similar solvents; although a cause-effect relationship could not be established (ATSDR, 1995a).

Several inhalation studies in rats involving various types of white spirits described minor behavioral changes and some neurochemical effects. Dearomatized white spirits (mostly alkanes) induced alterations in sensory-evoked potentials in rats

(ATSDR, 1995a; World Health Organization, 1996).

Kidney Toxicity from Products Containing Undecane: Animals exposed to vaporized white spirits and Stoddard solvent did not have kidney pathology (ATSDR, 1995a). In contrast, a C_{10}-C_{11} solvent fraction (mainly aliphatic) and JP-4 jet fuel caused the type of renal damage in male rats generally associated with the binding of xenobiotic compounds to α_{2u}-globulin (ATSDR, 1995a; World Health Organization, 1996).

Male Sprague-Dawley rats exposed to a white-spirit-like solvent (99% C_{10}-C_{12} aliphatics) showed a significant decrease in urine osmolality after 9.5 months of exposure. Increased activity of urinary lactate dehydrogenase was further noted as an indication of distal tubular dysfunction (Viau *et al.*, 1984).

Several human studies showed no association between exposure to Stoddard solvents and kidney dysfunction. However, the studies lacked sufficient exposure data to draw firm conclusions. A man who was exposed to Stoddard solvent by direct dermal contact and inhalation for 1 year developed glomerulonephritis (ATSDR, 1995a).

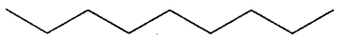
Hemapoietic System Effects from Stoddard Solvent: Studies of humans with aplastic anemia who were also exposed to Stoddard solvent have been reported, although a causal relationship was not established (ATSDR, 1995a).

Liver and White Spirits: Studies on humans exposed to white spirits and other chemicals in the workplace reported no histopathological changes in liver biopsies, however, some hepatic enzymes had elevated serum levels (ATSDR, 1995a).

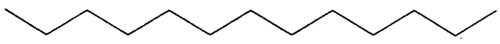
Structure-Activity Relationships: *N*-alkanes are thought to modulate carcinogenesis, especially because of their ubiquitous distribution and their tumor-promoting activity (Baxter *et al.*, 1981). Nonane [111-84-2] and tridecane [629-50-5], two hydrocarbons structurally related to undecane, were selected for review.

Undecane
1120-21-4

Nonane



Tridecane



No carcinogenicity bioassays conducted by modern regulatory standards are available for these compounds.

Nonane is a CNS depressant and a primary skin irritant. Chronic inhalation of nonane may cause altered neutrophils but no pulmonary lesions or axonopathies were noted (Cavender, 1994). Nonane was not mutagenic when tested in *Salmonella typhimurium* TA97, TA98, TA100, TA1535, and TA1537 with or without S-9 (CCRIS, 2002b).

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 16 2007

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Andrew M. Jaques, Director
n-Alkane VCCEP Consortium
American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Jaques:

Thank you for coordinating n-AlkaneVCCEP Consortium's sponsorship and assessment activities regarding n-decane, n-undecane, and n-dodecane in EPA's Voluntary Children's Chemical Evaluation Program (VCCEP). EPA appreciates the contributions of the Consortium and the member companies listed on the VCCEP Tier 1 assessment submission (Chevron Phillips Chemical LP, Sasol North America Inc., and Shell Chemical LP).

The purpose of this letter is to inform the Consortium and its member companies of EPA's VCCEP Tier 2 Data Needs Decision for n-decane, n-undecane, and n-dodecane. In formulating this decision, EPA has considered all available information, including the assessment and supplemental information provided by the Consortium and the report of the VCCEP Peer Consultation Panel that provided comments on the Consortium's assessment.

EPA has determined that the Tier 1 exposure assessment is complete but notes that there are some transparency issues and unaddressed uncertainties, particularly with regards to the Consortium's discussion of environmental fate. However, EPA does note that the Consortium's letter of December 6, 2005, to the Agency states that additional data on environmental fate and transport is being developed and will be provided to the Agency through the OECD SIDS program. Therefore, EPA does not recommend any Tier 2 exposure studies at this time for VCCEP.

EPA has also determined that all Tier 1 toxicity studies have been conducted, as well as several Tier 2 toxicity studies. Although EPA has identified several data gaps for Tiers 2 and 3 toxicity studies, EPA considers it unlikely that any new toxicity data would yield effects at levels substantially lower than the points of departure used in the current risk characterization such that it would be impacted in any significant way. Therefore, EPA does not recommend any additional Tier 2 or Tier 3 toxicity testing at this time for VCCEP.

EPA's Data Needs Decision document (see enclosure) will be posted to the VCCEP website, along with this decision letter, so that other stakeholders are informed of the status of this review.

Please contact Jim Willis, the Director of the Chemical Control Division in EPA's Office of Pollution Prevention and Toxics, if you have any questions or concerns associated with this Data Needs Decision. Jim can be reached at (202) 564-4760.

Sincerely,

Charles M. Auer
Director, Office of Pollution Prevention
and Toxics

Enclosure

VOLUNTARY CHILDRENS CHEMICAL

EVALUATION PROGRAM:

DATA NEEDS ASSESSMENT

OF n-ALKANES

Prepared By
Risk Assessment Division (7403M)
Economics, Exposure and Technology Division (7406M)
Office of Pollution Prevention & Toxics
April, 2007

Preface

Chemicals of potential concern to children's health are the subject of evaluation in the pilot Voluntary Children's Chemical Evaluation Program (VCCEP). VCCEP was developed to ensure that there are adequate publicly available data to assess the impact that industrial chemicals may have on children.

In August 1999, OPPT announced the initiation of a process in which it sought stakeholder input on all aspects of the VCCEP. OPPT held three public meetings and took comments on possible designs for a voluntary program. After considering all the comments of interested stakeholders, the pilot VCCEP was announced in a *Federal Register* notice on December 26, 2000. In the notice, OPPT asked companies that produce and/or import 23 specific chemicals to volunteer to sponsor their evaluation in Tier 1 of a pilot of the VCCEP. Thirty-five companies and ten consortia responded and volunteered to sponsor 20 of the chemicals.

The ultimate objective of the VCCEP is to ensure that there are adequate toxicity and exposure information available to assess the potential risks to children. A tiered approach is being pursued to gather the information, with each subsequent tier, of the three tiers, including more complex toxicology and exposure studies. Information from all three tiers may not always be necessary to adequately characterize the risk to children. The sponsor develops a chemical assessment at each tier of analysis. The assessment includes four sections: a summary of the toxicology information, a summary of the exposure information, a risk characterization, and a data needs assessment. The data needs assessment discusses the need for additional data, which could be provided by the next tier, to fully characterize the risks the chemical may pose to children.

During the public stakeholder meetings, it was proposed that an outside group of scientific experts should have the opportunity to provide comments on the data needs portion of the assessments. The approach adopted involves convening a group of scientific experts with extensive and broad experience in toxicity testing and exposure evaluations, as well as expertise in the specific chemical, referred to as a Peer Consultation Panel. The sponsor provides the assessments to an outside third party who is responsible for seeking input through the Peer Consultation Panel. The outside third party develops a summary of the panel's opinions and makes it available to the sponsor and the public.

OPPT reviews the sponsor's assessment and develops a response to the sponsor specifically on the data needs assessment. The response focuses primarily on whether any additional information is needed to adequately characterize the potential risks to children. EPA's response is sent to the sponsor and made available to the public.

Additional information regarding the Voluntary Children's Chemical Evaluation Program is provided in Appendix A and is available at http://www.epa.gov/chemrtk/vccep/index.htm.

In June 2004, the American Chemistry Council's n-Alkane VCCEP Consortium (ACC) submitted its Tier 1 assessment of the n-Alkane Category (decane, undecane, and dodecane) for the Voluntary Children's Chemical Evaluation Program (VCCEP). Errata and clarifications to

the text of the June 2004 assessment were submitted by the Consortium in September 2004. OPPT has reviewed the four components of the assessment, and where appropriate, has confirmed the accuracy of the toxicology and exposure information. EPA has also reviewed a report of a peer consultation panel that provided comments on the assessment; this report is available at www.tera.org. In addition, EPA contacted the sponsor for additional exposure information. This information was provided to EPA in letters dated December 6, 2005 and October 31, 2006. In the December 6, 2005 letter, the sponsor noted that additional data on fate and transport, and occupational exposure is being developed and will be provided to the Agency through the OECD SIDS process. In the letter dated October 31, 2006, the sponsor presented a summary of monitoring data for workers in n-alkanes production and distribution facilities.

1.0. Summary of EPA Recommendations for VCCEP

1. The Tier 1 exposure assessment is complete. For VCCEP, EPA does not recommend any Tier 2 exposure studies at this time.

2. All Tier 1 toxicity studies have been conducted, as well as several Tier 2 toxicity studies. For VCCEP, EPA does not recommend any additional Tier 2 or Tier 3 toxicity tests at this time.

2.0. Summary of Exposure Assessment

Production, Applications and Fate of Decane, Undecane, and Dodecane

The sponsor's assessment states that domestic n-alkane production in 1996 was approximately 762 million pounds. Import and export volumes are not given. The sponsor does not consider n-alkane production tied to hydrocarbon fuels, which may be up to 25% n-alkanes. The production of n-alkanes in fuels is likely to be orders of magnitude higher than the 762 million pounds cited by the sponsor.

The sponsor's assessment states that domestic n-alkane production capacity in 1996 was approximately 762 million pounds. A far greater (but unspecified) amount is produced in the refining of hydrocarbon fuels such as kerosene, diesel fuel, and home heating oil; the sponsor states that these sources are outside the scope of the submission.

The n-alkanes are used predominantly in the production of intermediate chemicals for the production of detergents and surfactants. The sponsor's assessment treats this use as the principal use for n-alkanes. Four types of specific processes are described, but no production data for each process are provided. The date of the information is not provided.

Decane, undecane, and dodecane are used primarily as chemical intermediates in the production of linear alkylbenzenes, which in turn are used in the production of surfactants. The processes that make use of n-alkanes are not perfectly efficient, so n-alkanes are entrained in the process waste stream. A small volume (less than 20,000 lb per year) is used as a laboratory

reagent. There are also many uses of fuels that contain these chemicals; the sponsor considered these uses to be outside the scope of the submission.

The physical, chemical, and environmental fate properties of n-decane, n-undecane, and n-dodecane are similar. The sponsor finds that these chemicals have a moderate to low vapor pressure, which decreases with increasing carbon-chain length. According to the sponsor's assessment, these chemicals are not likely to persist in the environment because they will largely partition to the air, where they will degrade via photo-oxidation. The sponsor notes that half-lives in air (during daytime) are calculated to be 9.2 hours for n-decane, 10.2 hours for n-undecane, and 11.5 hours for n-dodecane. [EPA notes that the estimated half lives in the atmosphere are actually as follows: n-decane, 11.5 hours; n-undecane, 10.2 hours; n-dodecane, 9.2 hours.] The sponsor finds that because these chemicals are biodegradable, the small portion that partitions to soil or sediment should not persist. The sponsor finds that these chemicals are insoluble in water and less dense than water, and that any releases of these alkanes to water should separate and volatilize to air. [EPA notes that the sponsor's discussion of environmental fate is oversimplified; see more details in Section 6.0, EPA Response to the Data Needs Assessment.]

Occupational Exposure

The sponsor's assessment presents monitoring data for workers for several scenarios found in a literature search. In section 6.4, the assessment includes no discussion about other exposed populations that are not covered by the literature search (e.g., occupational exposures during petroleum refining, n-alkanes processing, and formulation; and during paint, adhesive, carpet, wallpaper, and furniture manufacturing [industrial uses for products that contain n-alkanes, as described earlier in the submission]). Although the assessment seems to indicate that the Air Force base workers with exposures covered in section 6.4.6 (Air Force/Airline Industry/Re-Fueling) are the highest exposed population, the assessment does not explicitly state that this population is the highest exposed population. The assessment does not state whether monitoring data exist for workers in sponsor-controlled facilities nor does it present any existing data to demonstrate that workers in sponsor-controlled facilities have lower exposures than the Air Force base workers' exposures. A sponsor letter dated December 6, 2005 explained some issues related to the occupational exposure assessment, and this letter improved several aspects of transparency and completeness for the assessment. A summary of monitoring data for workers in n-alkanes production and distribution facilities were presented with a letter from the sponsor dated October 31, 2006. These data fill a key data gap and indicate that workers in these facilities all have exposures below detection limits for the n-alkanes.

Children's Exposure

The sponsor's assessment presents screening-level data in which certain exposure routes, such as oral ingestion, dermal contact, and exposure via breast milk, are assessed. The bounding

limits of exposure under these scenarios are found to be very low (3 or more orders of magnitude below the subchronic NOAEL). The sponsor's assessment does not consider these scenarios any further.

Some exposure scenarios are ignored because other exposure scenarios have a higher exposure concentration; it is not clear whether other factors, such as exposure frequency and exposure duration, are considered. This may result in the omission of a significant exposure pathway. For example, indirect exposure of mothers living near chemical plants is the basis of a breast milk study cited in the sponsor's assessment, but this pathway is eliminated from consideration.

The sponsor's assessment rules out all exposure routes but the inhalation route on the basis of existing data. To eliminate the non-inhalation scenarios, the report provides upper-bound estimates of exposure from the oral, dermal, and breast milk routes. Oral exposure is estimated by calculating the exposure for an infant consuming drinking water containing n-alkanes at the saturation level. Dermal exposure is estimated through a modeled occupational exposure of an expectant mother exposing both hands to fuel for 1 hour per day for 250 days per year. For breast milk, n-alkane concentrations are estimated using an existing exposure study. The concentration of n-alkanes in breast milk are estimated by comparing peak heights for n-alkanes with those of other analytes.

The sponsor's assessment cites no exposure studies specific to children. Instead, the study uses data for environments in which children are likely to spend time, or in which prospective parents are likely to have an unusually high degree of exposure. Some potential exposure scenarios are removed from consideration because other scenarios would tend to produce higher levels of exposure. For example, exposure to individuals living near the perimeter of an airport or Air Force base may have a higher level of exposure than the general population, but no data are available. This scenario is eliminated because a study cited in the sponsor's assessment indicates a low level of exposure for workers on the airport/base property, which would typically be higher than exposure levels outside the perimeter. Other studies cited in the sponsor's assessment provide exposure point concentrations for the interiors of passenger airplanes, automobiles, schools, offices, and photocopy centers. Available exposure studies indicate that emissions from furniture and photocopying may result in elevated VOC levels in offices and photocopy centers, and that some workers in the Air Force and airline industry may also be exposed. However, the assessment does not present any estimates of environmental releases from high-release industrial processes (e.g., some manufacturing, processing, or industrial uses of these chemicals), and the assessment does not present a rationale for exclusion of such estimates from the assessment.

In the sponsor's assessment, the painting and refueling scenarios have the highest concentrations among the occupational scenarios, and residential indoor air has higher concentrations than outdoor air or the interiors of vehicles. As a result, the exposure scenarios considered in the sponsor's risk assessment include:

1) Chronic exposure of infants and children to indoor air;
2) Chronic exposure of prospective parents to indoor air;

3) Short-term exposure of infants and children in a newly painted home;
4) Short-term exposure of prospective parents in a newly painted home; and
5) Prospective parents with occupational exposure in the painting trade and in airport refueling operations.

The finding of these scenarios in a literature review was the only rationale presented for the selection of these scenarios for the risk assessment. For each of these scenarios, likely exposure concentrations are estimated using existing exposure studies.

3.0. Summary of Hazard Assessment

Category Justification

The sponsor has suggested that the C_{10}-C_{12} n-alkanes be treated as a category. The sponsor contends that the similar physical/chemical properties and toxicity profiles justifies the category approach. The alkanes in this group are all short homologous series of hydrocarbons, liquids at room temperature with low vapor pressures, and are insoluble in water. According to the sponsor's report, similar systemic effects have been reported in repeat-dose animal toxicity studies for all three alkanes in the category. Increased liver weight and changes in male rat kidney were observed following repeated oral exposures; irritation effects were observed from repeated dermal or inhalation exposure. Toxicity data from the individual n-alkanes and n-alkane process streams is also provided in the submission; additional toxicity information on complex mixtures of linear, branched, and cyclo-alkanes in the same carbon range was provided by the sponsor as supporting information. Table 1 below provides a summary of the available Tier 1 toxicity data. Check-marks indicate data are available; 'x' marks indicate no data are available. Where data for the individual n-alkane did not exist, the sponsor used data from other individual n-alkanes or commercial products as read-across to fill in any data gaps for the chemical.

Table 1. Summary of Existing Tier 1 Toxicity Studies

Tier 1 Toxicity Studies		Decane (C_{10})	Undecane (C_{11})	Dodecane (C_{12})	Other Alkanes*
Acute Toxicity	Oral	✓	✓	✗	✓
	Dermal	✗	✗	✗	✓

	Inhalation	✓	✓	✓	✓
Genetic Toxicity (In Vitro)	Bacterial	✓	✓	✗	✓
	Cytogenetics	✓	✓	✓	✓
Genetic Toxicity (In Vivo)	Micronucleus	✗	✗	✗	✓
Repeat-Dose Toxicity		✓	✓	✗	✓
Combined Repeat-Dose Toxicity with Reproductive and Developmental Toxicity Screens		✓	✓	✗	✓

*Consists of other individual n-alkanes or commerical products such as: n-nonane, n-tridecane, or n-tetradecane ; and mixtures of multiconstituent alkane (C_9-C_{13},C_{10}-C_{13}, C_{11}-C_{14} ,C_{12}- $_{14}$, C_{14}-C_{17}) products consisting of n-, iso-, and cyclo- alkanes.

Toxicokinetics of n-Alkanes

Absorption and Distribution

Inhalation

n-Alkanes enter systemic circulation either as vapor or aerosol, depending upon the vapor pressure at a given temperature, primarily through the inhalation route of exposure. In general, aliphatic hydrocarbons which have lower vapor pressure and lower blood:air partition coefficients than aromatic hydrocarbons, are less efficiently taken up after inhalation than are aromatic hydrocarbons. In rats, saturated hydrocarbons are absorbed to a lesser extent by inhalation than are unsaturated hydrocarbons.

The inhalation kinetics of C_6-C_{10} hydrocarbons were studied by exposing rats (strain and sex not specified) to an average of 100 ppm of each substance for 3 consecutive days and then measuring the concentration of hydrocarbon in the blood, brain, liver, kidney and adipose tissue. The distribution of n-decane by Day 3 was as follows (μg/mol/kg, mean ± SD): blood (6.8 ± 0.5), liver (45.9 ± 3.9), brain (60.2 ± 12.7), kidney (77.7 ± 27.3) and adipose tissue (1230 ± 63). The lower concentrations seen in the liver when compared to the brain and kidney may be due to different rates of metabolic elimination in the rat liver or to differences in liver partitioning between n-decane and other hydrocarbons which included napthenes and aromatics. The overall conclusion was that n-alkanes show very low concentrations in the blood, relatively elevated concentrations in brain and the potential to accumulate in adipose tissue with repeated exposures.

In a second study, rats (strain and sex not specified) were exposed to 0.5, 1.5, or 5 g (approximately 85, 260, or 860 ppm) n-decane/m^3. The concentration of n-decane in the blood

after a single 8 hour exposure to air, 0.5, 1.5, or 5 g/m^3 was <30 (the detection limit), 567, 1173, and 73,333 ng/ml respectively. After a single 8 hour exposure, the concentration of n-decane in the brain was approximately 12-23X higher than the concentration in blood.. The peak brain/blood ratio after a single 8 hour exposure reaches its maximum at 2 hours and begins to decline through 8 hour post exposure in both blood and brain. No concentrations of n-decane in the brain or blood were given to support these statements.

The distribution of n-nonane, n-decane, n-undecane and other hydrocarbons was studied in brain, blood and fat tissue of rats (strain and sex not specified) after repeated exposure to dearomatised white spirit. n-Nonane, n-decane and n-undecane comprised 3.6, 16.6, and 9.6% respectively of the dearomatised white spirits (DAWS) used in this study. Rats were exposed by whole-body inhalation to air, 400 ppm, and 800 ppm DAWS vapors for 6 hrs/day, 5days/week for 1, 2, or 3 weeks. The concentration of n-nonane, n-decane and n-undecane in blood and brain was nearly the same after 1, 2, and 3 weeks of exposure. Two hours after the end of exposure, the concentration of n-decane decreased to about 25% of the highest concentration in blood and 50% in the brain. Concentrations of n-nonane, n-decane and n-undecane in adipose tissue increased during the 3 weeks of exposure and decreased very slowly after the end of exposure. Post exposure decay in blood and brain could be separated into two phases; half-lives in blood were approximately 1 and 8 hours and half-lives in brain were approximately 2 and 15 hours. In fat tissue, only one slope with a half-life of approximately 30 hours was identified. Three weeks exposure to n-decane and n-undecane resulted in fat:brain:blood concentration coefficients of 260:3:1. The study suggests similar and independent toxicokinetics for n-nonane, n-decane and n-undecane. No numbers were presented to support any of these conclusions.

Ingestion and Intravenous

The mechanism of GI absorption is not understood, but it is likely that the alkanes pass predominantly into the lymphatic system before entering into the blood stream. However, direct entry into the blood system may occur especially for n-alkanes of shorter chain lengths.

It has been shown that the major site of absorption in rats (strain and sex not specified) fed intragastrically with a mixture of hydrocarbons (the mixture was not further identified) of varying chain lengths was the small intestine and that the rate of absorption was inversely related to carbon chain length. No numbers were presented to support this conclusion.

Intravenous experiments have shown that after entering the blood, there is a rapid transport in the liver followed by redistribution and temporary deposition in fatty tissues, such as adipose tissue. Once in fat, release is slow and, depending on dose, levels can be detected after one month. No experimental details were given and no numbers were presented to support the conclusions stated.

Metabolism and Excretion

The metabolism of C_{10}-C_{12} n-alkanes has not been well characterized. In general, identification of specific metabolites and monitoring of enzyme activities indicates that biotransformation is mediated by hepatic microsomal cytochrome P-450 system. Metabolism of n-alkanes is rapid and proceeds to either 1- or 2-hydroxydecane. The hydroxydecanes are then further oxidized to carboxylic acids which are then oxidized to CO_2. An alternative pathway has been detected with n-decane in which n-decanoic acid can be further oxidized to 10-hydroxydecanoic acid prior to further oxidation. Overall, it is likely that little excretion occurs via the urine, although unspecified amounts of partially oxidized conjugated metabolites do appear in the urine. In one experiment, several cyclized derivatives (lactones) were detected in the urine from unlabelled n-nonane, but the amounts of these derivatives could not be quantified. No further experimental details, e.g., species, amount of n-nonane administered, collection times after treatment, etc. were given. An initial omega hydroxylation is probably the rate limiting metabolic step since no significant accumulation of metabolites in tissues has been reported with n-alkanes of various chain lengths. The hydroxylated metabolites are also products of normal body metabolism. Therefore, they are likely to be used in various bodily biosynthetic routes and for generating ATP. CO_2 generated from n-alkane metabolism can be reincorporated in the process of gluconeogenesis, or eliminated through the lungs via exhalation.

Toxicity Data in Humans

There are no epidemiology studies on individual n-alkanes. In addition, there are very limited human data on hydrocarbon solvents and jet fuels which contain n-decane, n-undecane, and n-dodecane as components. There are many limitations to these reports. In addition, hydrocarbon solvents are comprised of many chemical constituents, and the n-alkanes cannot be directly associated with adverse health outcomes reported in the literature. Case reports of chemical pneumonitis resulting from poisoning of children through accidental ingestion of hydrocarbons led CPSC to require child resistant packaging on products containing 10% or more hydrocarbons.

Toxicity Data in Animals

Mutagenicity

Genetic toxicology studies including bacterial and mammalian mutagenicity studies, cytotoxicity studies and DNA adduct formation have been performed on n-decane, n-undecane, and n-dodecdecane, the members of the category, and on the lower and higher structural homologues, n-nonane and n-tetradecane, and on a C_{10}-C_{13} n-alkane product and on an aliphatic hydrocarbon solvent for comparative purposes.

1-Decane (97% pure), tetradecane, nonane, n-decane, n-undecane and the C_{10}-C_{13} n-alkane product were all negative when tested for the ability to induce mutation in *Salmonella typhimurium* in the Ames assay both with and without metabolic activation. n-Undecane was

also negative when tested for the ability to induce mutation in *Escherichia coli* WP2uvrA both with and without metabolic activation. Purity of chemicals other than 1-decane was not given.

n-Decane, n-dodecane and n-tetradecane were tested for their ability to enhance the mutagenic activity of methylazoxymethanol in the V79 line of Chinese hamster lung cells. The tests were performed without metabolic activation only. The three alkane compounds were negative, but the activity of methylazoxymethanol was enhanced by all three.

1-Decane (97% pure) did not induce chromosomal aberrations in the V79 line of Chinese hamster lung cells and n-undecane did not induce chromosomal aberrations in the IU line of Chinese hamster lung cells. Both tests were performed with and without metabolic activation.

The C_{10}-C_{13} n-alkane product was tested for its ability to form micronuclei in the bone marrow of male and female CD-1 mice after a single administration by oral gavage of 0, 1.0, 2.5, and 5.0 g/kg doses. There was no increase in micronuclei at any dose tested. The NOAEL was 5.0 g/kg; the LOAEL was not established.

n-Decane and n-dodecane were tested for their ability to form DNA adducts in the skin of C_3H mice. Twenty-five μl of test agent was applied to the skin either as a single application or as three daily applications on successive days. Neither chemical induced DNA adducts under either treatment regimen nor did either chemical enhance the in vivo DNA adduct forming ability of benzo(a)pyrene.

Acute Toxicity

Acute toxicity studies were performed on n-decane, n-undecane and n-dodecane, which are the members of the category, and on n-nonane and n-tetradecane, which are lower and higher structural homologues, respectively. Complex mixtures containing various members of the category-related linear homologues were included for comparative purposes.

The rat (strain and sex not specified) oral LD_{50} of n-decane and n-undecane, the only two members of the category tested for acute oral toxicity, was >5.0 g/kg and >2.0 g/kg, respectively. LD_{50} values for the homologues n-tetradecane, C_{10}-C_{13} alkanes, C_{12}-C_{14} alkanes, and C_{14}-C_{17} alkanes were all >5.0 g/kg. Except for one animal treated with C_{10}-C_{13} alkanes, no mortality occurred in any study including those with n-decane and n-undecane. Clinical signs reported included soft stool, ano-genital staining, piloerection, alopecia, and unthrifty coat. The clinical signs were reported to be associated with "some studies", but which studies were not specified so they could not be associated with a particular chemical or chemicals. Necropsy data were not reported so target organs, if any, could not be identified.

The 4-hour acute rat (strain and sex not specified) LC_{50} for n-nonane was 16,753 mg/m^3. Clinical signs included salivation, lacrimation, tremors, convulsions and death. No effects were observed at 4,600 mg/m^3. No necropsy data were reported so target organs, if any, could not be

identified. In a second study, rats (strain and sex not specified) were exposed to n-nonane at four concentrations up to near saturation (27,642 mg/m^3) and to n-decane, n-undecane, n-dodecane and n-tetradecane at near saturation concentrations of 7,951, 2,693, 987 and 309 mg/m^3, respectively. The LC_{50} for n-nonane was 23,386 mg/m^3; no deaths or overt signs of toxicity occurred at 12,638 mg/m^3. n-Decane, n-undecane, n-dodecane and n-tridecane did not produce any overt signs of toxicity. All studies were conducted at the highest vapor concentration practically attainable due to vapor pressure limitations. n-Nonane was the only substance that was sufficiently volatile to create a vapor concentration at which some deaths occurred, i.e., the LC_{50} of n-nonane equals 16,753 mg/m^3. The LC_{50}'s of the other substances tested, n-decane, n-undecane, and n-dodecane are all greater than the highest vapor concentration tested, e.g., in the range of greater than 3,600 to greater than 12,400 mg/m^3.

Repeated Dose Toxicity

Members of the n-alkane category (n-decane and n-undecane) have been studied in limited repeat-dose oral and inhalation studies in rats and mice. There are additional studies of n-nonane that were used as a structural analog by the sponsor. There were no studies for n-dodecane alone, but there are studies of mixtures of petrochemicals which contain C_{10} - C_{12} as well as other linear, branched and cyclic alkanes.

There are few studies of the dermal toxicity of chemicals in this category. There have also been dermal studies of some analogs of the chemicals in this group. Most demonstrate irritation and direct effects on the skin. Some have systemic toxicity as well.

Oral

Commercial n-decane (approx. 97% pure) was tested in a combined repeat dose developmental/reproductive toxicity test in Sprague Dawley rats using gavage administration. Groups of 10 male and 10 female rats were dosed with 0, 25, 150, or 1000 mg/kg-day. Males were treated from 14 days prior to mating, through the mating period and then killed. Females were treated from 14 days prior to mating, through mating and pregnancy until day 4 of lactation. At 150 mg/kg-day, irritation of the nonglandular mucosa of the stomach was observed. The authors considered this stomach irritation a result of gavage administration and not indicative of toxicity of the n-decane. There was no other evidence of adverse effects on clinical observations, organ weights, gross or microscopic pathology. The NOAEL for systemic toxicity is 1000 mg/kg-day, the highest dose tested.

Undecane ($\geq$ 99% pure) was tested in a combined repeat-dose developmental/reproductive toxicity test in Sprague Dawley rats using gavage administration. Groups of 12 male and 12 female rats were dosed with 0, 100, 300, or 1000 mg/kg-day. Males were treated for 46 days. Females were treated from 14 days prior to mating, through mating and pregnancy until day 3 of lactation. Clinical signs of toxicity including salivation were observed in males and females in the 300 and 1000 mg/kg-day dose groups. Statistically

significant decreased body weight gain was observed in males at 1000 mg/kg-day. Relative liver weights and relative and absolute thymus weights were increased in males at 1000 mg/kg-day. Absolute and relative liver weights were increased in females at the 1000 mg/kg-day dose group. No histopathological effects were observed. High dose males had hematological changes. The NOAEL was 100 mg/kg-day.

An unpublished 90-day study of C_{11}- C_{14} multi-constituent alkanes (a mixture containing n-alkanes as well as branched and cycloparaffins) treated Sprague-Dawley rats with 100, 500 or 1000 mg/kg-day by gavage. There were 10 animals per sex per dose. Male rats showed kidney enlargement and signs of toxicity consistent with α2μ-globulin induced nephropathy at mid and high doses (500 or 1000 mg/kg-day). However, the study did not include all the necessary testing to prove α2μ-globulin induced nephropathy. The LOAEL of 500 mg/kg-day is based on significant increases in relative liver weights in both male and female rats and centrilobular hepatocellular hypertrophy in females. The NOAEL is 100 mg/kg-day. A study with the same design testing C_{10}-C_{13} multi-constituent alkanes (a mixture containing n-alkanes as well as branched and cycloparaffins) at concentrations of 500, 2500 and 5000 mg/kg-day for 90 days. Male rats showed kidney enlargement and signs of toxicity consistent with α2μ-globulin induced nephropathy at mid and high doses (2500 or 5000 mg/kg-day). However, the study did not include all the necessary testing to prove α2μ-globulin induced nephropathy. The LOAEL of 2500 mg/kg-day is based on significant increases in relative liver and kidney weights in both male and female rats, and centrilobular hepatocellular hypertrophy increasing in incidence and severity with dose. Gross and microscopic irritation of the GI tract were noted but may be due to the irritation of a high bolus dose. Fourteen animals died during the experiment; of which 13 deaths were attributed to dosing trauma or aspiration of the test material.

Inhalation

In a 13-week inhalation study, albino Harlan-Wistar male rats (25 per group) were exposed for 6 hours/day, 5 days/week to 1.9, 3.1, or 8.4 g/m^3 (360, 590, or 1600 ppm) of n-nonane. Two rats died in the low dose group but necropsy revealed suppurative bronchopneumonia. At 1600 ppm, 2 rats died during the first day of exposure. Rats in the high-dose group exhibited clinical signs of toxicity including salivation, mild loss of coordination, and tremors throughout the first 4 days of exposure. During 6 hour exposures for the remainder of the study, rats in the 1600 ppm group exhibited salivation and lacrimation. Body weights or body weight gains were significantly lower than controls on day 3, 17, 32, 46 and 61. The NOAEL was 3.1 g/m^3(590 ppm) and the LOAEL based on clinical signs and body weight reductions is 8.4 g/m^3(1600 ppm).

Rats (number [maybe 41-43??], strain and gender not specified) were exposed to 3.1 g/m^3 (540 ppm) n-decane for 18 hours per day for seven days per week for 91 days as a comparative control in a study of aromatic-rich petroleum distillates toxicity. Rats showed an increased in body weight gain and a decrease in WBC compared to controls at 57 days. At 123 days (which may represent 91 days exposure plus a 1 month recovery) there was an increase in body weight gain and an increase in WBC. No other significant changes were observed in hematologic measures or gross or microscopic pathology of other organs. The study tested only one concentration and the report lacks critical details.

Male and female Sprague-Dawley rats were exposed to de-aromatized white spirit, DAWS (a mixture of $\leq$ 0.5% aromatic, 58% straight and branched alkanes, and 42% cycloalkanes) or C_{10}- C_{11} isoparaffinic hydrocarbon, IPH, for 6 hours/day, 5 days /week in a 12-week inhalation study. Two concentrations of each mixture were tested (300 ppm and 900 ppm) with 15 rats per sex per group. At 1.9 and 5.7 g/m^3(300 ppm and 900 ppm), DAWS treated male rats showed signs of kidney toxicity (regenerative tubular epithelia and dilated tubules) consistent with $\alpha 2\mu$-globulin induced nephropathy. However, the study did not include all the necessary testing to prove $\alpha 2\mu$-globulin induced nephropathy. Other organ systems (respiratory, cardiac, GI, hematological, skeletal/muscular, hepatic) showed no signs of chemical-specific effects at either dose of DAWS. At 1.8 and 5.5 g/m^3 (300 and 900 ppm), IPH treated male rats showed signs of kidney toxicity consistent with $\alpha 2\mu$-globulin induced nephropathy. However, the study did not include all the necessary testing to prove $\alpha 2\mu$-globulin induced nephropathy. Males also had decreased body weight at both concentrations after 6 weeks and a 10% decrease in erythrocyte counts. The hematological effect was not dose-related and discounted by the authors. Male and female rats had increased liver weights at 5.5 g/m^3 (900ppm). The LOAEL is 1.8 g/m^3(300 ppm) for IPH.

Dermal

Over a one year period, n-decane was applied to the backs of 20 male C3H mice using a paint brush (not specified if skin shaved, prepared, or covered) 3 days per week on alternate days for approximately 150 applications per mouse. Most adverse changes were localized. In gross pathology it was reported the skin was thick dry and scaly. Microscopic examination of the skin revealed fibrosis, pigmentation, ulceration, hyperkeratosis, and perikeratosis. Microscopic kidney, spleen and lung adverse changes were also reported. However, it is not clear from the study report of procedures if inhalation and oral (licking) exposure were prevented. This study was designed to test the toxicity of aromatic-rich petroleum distillates and n-decane was included in this study as a comparative control. Apparently, only one dose of n-decane was tested and not clearly quantified. Study details are lacking.

Neurotoxicity

In a combined repeat-dose oral reproductive/developmental toxicity screening study with commercial decane in rats exposed to doses as high as 1000 mg/kg/day, startle reflex, open field test, and forelimb grip reflex performance in adult animals were evaluated and found to be comparable to controls. Functional observational battery, motor activity, and visual discrimination following n-decane exposure were evaluated in another toxicity study in rats. Four groups of 4 male WAGR/RijCrlBR rats were administered 0, 0.5, 1.5, and 5 g/m^3 n-decane 8 hours/day for 3 consecutive days by the inhalation route. Following the third exposure period, significant reduction in forelimb grip strength, and mild disturbances in measures of learned performance and performance speed were observed at the highest concentration. Evaluation of neurohistopathology was not conducted. No other effects were reported. These effects appeared to be reversible, one day post-treatment.

A 90-day repeat dose toxicity study with n-nonane was conducted in male rats. Four groups of 25 male Albino Harlan-Wistar rats were administered 0, 1.9, 3.1, and 8.4 mg/m^3 n-nonane by inhalation 6 hours/day, 5 days/week for 13 weeks. Salivation, lacrimation, mild loss of coordination, and fine tremors were observed during the first 4 days of exposure at concentrations of 8.4 g/m^3, the same concentration that also produced mortality.

A 28-day repeat dose dermal toxicity study with a neuropathological evaluation of the peripherial and central nervous system with C_{12}-C_{14} normal paraffins was conducted in rabbits. Four groups of 5 males and 5 females New Zealand White rabbits were administered 0, 100, 500, and 2000 mg/kg C_{12}-C_{14} normal parrafins by the dermal route 6 hours/day, 7 days/week for 28 days. No marked abnormalities or degenerative neuropathological changes were observed following histopathology. Hypopnea, hypoactivity, decreased righting reflex and staggered gate were observed; however, it was uncertain if these effects were truly related to exposure since severe dermal irritation hindered animal movement, in fact, the 2000 mg/kg group had to be euthanized early due severe dermal irritation. The authors reported a NOAEL of 500 mg/kg for neurotoxicity.

Cancer

Purified n-alkanes have not been tested for carcinogenicity via oral or inhalation exposure. In studies of mice skin tumors, C_{10} - C_{14} n-alkanes have been shown to have promotion but not initiation activity. The skin tumor promoting activity appears to be secondary to skin irritation.

Reproductive/Developmental Toxicity

No definitive developmental or two-generation reproductive toxicity studies with any of the n-alkanes in this category (decane, undecane, dodecane) were located. A review of the numerous repeat-dose toxicity studies in adult animals did not report effects on any reproductive organs, although it is not clear if these organs were even evaluated in those studies. The only evidence of reproductive organ effects following repeated exposures was reported in a NTP study in rats and mice with Stoddard Solvent, a low aromatic hydrocarbon solvent containing C_{10}-C_{14} n-, iso-, and cycloalkanes, but Stoddard Solvent is not considered to be structurally related to the n- alkanes in this category. Three screening level studies were located that evaluated developmental and/or reproductive toxicity of decane, undecane, and a mixed alkane solvent; two combined repeat-dose reproductive/developmental toxicity screening studies, and a segment II teratology study. These studies were considered relevant and are summarized below.

A combined repeat-dose reproductive/developmental toxicity screening study has been conducted with commercial decane (>97% n-decane, or C_{10}) in Sprague-Dawley rats by the oral route. Doses of 0, 25, 150, or 1000 mg/kg/day commercial decane was administered via gavage to 10 male rats 14 days prior to and during mating, and to10 female rats 14 days prior to mating;

continuing throughout mating, gestation, and day 4 of lactation for one generation. Parameters assessed included adult body weights, food consumption, maternal body weight gains, gestation length, pregnancy rates, mating, conception, viability index, post-implantation losses, fertility and gestation indices, pup body weights, external examination of pup abnormalities, number of live and still births, pup mortality, and pup sex. Reproductive organ weights and gross and histologic examination of the reproductive tract, with special emphasis on stages of spermatogenesis and testicular cell structure, was also conducted. No signs of either maternal or reproductive/developmental toxicity were observed. Mating, conception, gestation length, litter size, offspring survival, gestation and postnatal survival indices, percent pre- and post-implantation losses, pup body weight, and pup sex ratio were comparable to controls across all dose groups. A slight increase in the mean mating time compared to controls was observed in the high-dose group only. Since the increase was not statistically significant and was within the range for historical controls, the authors did not consider this effect to be treatment-related. Likewise, a decrease in the fertility index was also observed; however, the decrease was not statistically significant and did not show a dose-response, therefore the authors did not consider this effect to be treatment-related. Under the conditions of the study, the authors considered the NOAEL for toxicity to parents and offspring to be 1000 mg/kg/day.

In another combined repeat-dose reproductive/developmental toxicity screening study, 4 groups of 12 male and 12 female Sprague-Dawley rats were administered 0, 100, 300, and 1000 mg/kg/day undecane ($\geq$ 99%, or C_{11}) by oral gavage for one generation: 14 days prior to and during mating in both sexes; continuing 46 days in the males, and through gestation to day 3 of lactation in the females. Endpoints evaluated included clinical signs of toxicity, adult body weights, food consumption, blood chemistries, organ weights and histopathology, offspring body weight and viability, and various other reproductive and pregnancy parameters such as observations on deliveries and maternal behavior; and indices for mating, fertility, gestation, and nursing. Salivation in males and females was observed at 300 and 1000 mg/kg/day. In the adult males, statistically significant decreases in body weight were seen at 1000 mg/kg/day. Statistically significant increases in body weight were seen in high-dose adult females during lactation. In males, food consumption was decreased at 300 and 1000 mg/kg/day during the first half of the administration period, but increased at 1000 mg/kg/day during the second half. In females, food consumption was increased in high-dose females later in the pregnancy and into lactation. Decreases in hemoglobin and albumin concentrations; increases in white blood cells, in $\alpha 2\mu$-globulin, GPT, cholinesterase and total cholesterol; and increases in relative liver and thymus weights were observed in high-dose males. Increases in absolute and relative liver weights were observed in high-dose females. No gross macroscopic or histopathologic effects were noted at any dose level. A slight decreased body weight gain in both male and female offspring in the 1000 mg/kg/day dose group was observed. No other effects on the offspring or on any other reproductive parameters were reported. Under the conditions of the study, the authors concluded that the NOAEL for parental toxicity was 1000 mg/kg/day and the NOAEL for developmental/reproductive toxicity was 300 mg/kg/day.

A third study evaluated the developmental toxicity of a solvent consisting of C_9-C_{13} mixed alkanes (n-, iso-, and cycloparaffins) using the FDA 1966 Segment II Teratology protocol. In that study, three groups of 21 mated Sprague-Dawley rats were administered 0, 300, and 900

ppm mixed alkanes by whole-body inhalation 6 hours/day from gestation days 6-15. An additional group receiving 400 mg/kg/day of acetylsalicyclic acid via gavage on gestation days 6-15 served as the positive control. Maternal body weights, body weight gains; numbers of corpora lutea, implantations, resorptions, fetuses per dam; fetal and litter weights, and crown-rump distances were evaluated. Pregnancy rate, mortality, body weight gain and gross postmortem examinations were all unaffected by treatment. The only effect noted was a slight increase in lacrimation during the treatment and post-treatment period in high-dose females. No effects on any of the fetal/developmental parameters were reported. Under the conditions of the study, the authors concluded that NOAEL for both maternal and developmental toxicity was 900 ppm (or 866 ppm mean actual; 5 g/m^3).

Developmental Neurotoxicity

Although studies designed to specifically evaluate neurotoxicity in offspring for any of the n-alkanes in this category were not located, some endpoints of neurotoxicity were either evaluated or observed in several of the repeat-dose toxicity studies in adult animals. In a combined repeat-dose oral reproductive/developmental toxicity screening study with commercial decane in rats exposed to doses as high as 1000 mg/kg/day, startle reflex, open field test, and forelimb grip reflex performance in adult animals were evaluated and found to be comparable to controls. Significant reductions in forelimb grip strength, and mild disturbances in measures of learned performance and performance speed were observed in rats exposed to 5 g/m^3 n-decane 8 hours/day for 3 consecutive days by the inhalation route. Salivation, lacrimation, mild loss of coordination, and fine tremors were observed during the first 4 days of exposure in adult male rats repeatedly exposed to n-nonane (C_9) by the inhalation route at concentrations of 8.4 g/m^3, the same concentration that also produced mortality. A 28-day repeat dose dermal toxicity study with a neuropathological evaluation of the peripherial and central nervous system with doses as high as 2000 mg/kg C_{12}-C_{14} normal paraffins was conducted in New Zealand White rabbits. No marked abnormalities or degenerative changes were observed; however, severe dermal irritation made in-life neurological evaluations difficult, although hypopnea and hypoactivity were observed.

Immunotoxicity

Studies designed to specifically evaluate immunotoxicity for any of the n-alkanes in this category were not located; however, possible signs of immunotoxicity were observed in several of the repeat-dose toxicity studies in adult animals. For example, increases in white blood cells and in thymus weights were observed in male rats repeatedly exposed by the oral route to 1000 mg/kg/day C_{11} (n-undecane). Extramedullary hematopoiesis and enlargement of the spleen, increases in neutrophils, and decreases in lymphocytes were observed in female rabbits repeatedly exposed by the dermal route to 2000 mg/kg n-hexane (reference control group in the rabbit 28-day repeat-dose toxicity study). Possible alterations in white blood cell counts were observed in rats exposed by the inhalation route to 3100 mg/m^3 n-decane; no changes were observed in the polymorphonuclear leukocyte-lymphocyte ratio or on the bone marrow; however, the study design for this particular study was flawed and the results uncertain. Male

mice exposed by the dermal route to a 100-150 mg/application of n-decane showed pathological changes in the spleen; hematology was unremarkable.

4.0. Risk Characterization

A Margin of Exposure (MOE) or Margin of Safety (MOS) approach was used by the sponsor for non-occupational exposure scenarios; occupational exposures were compared with the proposed Occupational Exposure Limit (OEL). The sponsor considered the inhalation route to be the most relevant exposure route for human risk assessment for the n-alkanes in this category. Neither the oral nor the dermal routes were considered a relevant human exposure scenario by the sponsor. The sponsors estimated health benchmarks based on the animal toxicity studies and used the same health benchmarks for each of the chemicals in the category. For the acute inhalation health benchmark, the sponsor used an inhalation concentration of 5 g/m^3, a concentration at which no lethality would be expected. For the subchronic inhalation health benchmark, based on a number of repeat-dose inhalation toxicity studies on individual n-alkanes, and on mixed products, an inhalation concentration of 1 g/m^3 for 6 hrs/day, 7 days/week for 13 weeks was derived by the sponsor as the lowest NOAEL point of departure. For the inhalation developmental/reproductive toxicity health benchmark, the sponsor used 5 g/m^3, the concentration at which inhalation exposure to a complex mixture of C_9-C_{13} alkanes consisting of n-, iso-, and cycloparaffins showed no evidence of developmental toxicity. The sponsor also used an inhalation developmental/reproductive toxicity health benchmark that combined both the inhalation and oral (adjusted to inhalation concentrations) routes in the range of 2-7 g/m^3. And finally, for chronic health benchmarks, the sponsor used the RfC and RfD generated by the Total Petroleum Hydrocarbon Working Group (TPHCWG) that used combined data from subchronic and developmental toxicity studies on the various fractions including the C_{10}-C_{12} aliphatic fraction. A chronic RfC of 1000 $\mu g/m^3$ and a chronic RfD of 0.1 mg/kg/day were derived. The 8-hour Occupational Exposure Limit (OEL) of 1,200 mg/m^3 was used as the point of departure to assess occupational exposures. All of these inhalation health benchmarks are summarized from the sponsor's assessment in Table 2 below.

Table 2. Inhalation Health Benchmarks from the Sponsor's Assessment

Benchmark	**Value**
Inhalation Subchronic NOAEL of 1 g/m^3 (adjusted to continuous exposure)	2.5×10^5 $\mu g/m^3$
Chronic Reference Concentration (RfC) (Total Petroleum Hydrocarbon Working Group)	1000 $\mu g/m^3$
Acute Toxicity (Short Term Exposure)	5.0×10^6 $\mu g/m^3$

Inhalation Developmental/Reproductive NOAEL (Adjusted to continuous exposure)	1.25×10^6 $\mu g/m^3$
Occupational Exposure Limit (8-hour)	1.20×10^6 $\mu g/m^3$

The sponsor calculated MOEs and MOSs for the following exposure scenarios for infants, children, and adults: chronic exposure at home, short term domestic exposure during renovation, and occupational exposures for prospective parents. Since inhalation exposure was considered the only significant exposure route by the sponsor, both occupational and non-occupational MOEs were calculated by dividing the inhalation subchronic health benchmark value of 2.5×10^5 $\mu g/m^3$ (determined by the sponsor as the most conservative health benchmark) in Table 2 above by the combined exposure concentrations (in $\mu g/m^3$) for these selected exposure scenarios. The MOSs were calculated by dividing either the RfC or the OEL (referenced above) by the combined exposure concentrations. All of these are summarized in Table 3 below. Upper bound estimates were based on studies reporting the highest levels that may or may not have discriminated between normal and branched alkanes. The inhalation benchmark dose did not take into account the higher dose to a child based on inhalation rate and body weight. The age-range for children was not indicated in the sponsor's report.

Table 3. MOEs and MOSs for Varying Exposure Scenarios from the Sponsor's Assessment

Receptor	**Representative MOE**	**Upper Bound MOE**	**Representative MOS**	**Upper Bound MOS**
Margin of Exposure for Chronic Exposure at Home				
Children and Prospective Parents	6,000	1,900	24	8
Margin of Exposure for Short Term Domestic Exposure During Renovation				
Children and Prospective Parents	2,000	275	8	1.1
Margin of Exposure for Occupational Exposure for Prospective Parent Occupationally Exposed in Aviation Fuel Related Operations Based on the OEL				
8-Hour Exposure (adjusted for continuous exposure)	200	65	237	71

The potential for aggregate exposures from an occupationally exposed parent returning home to a freshly painted house and breast feeding an infant was also considered by the sponsor. In this particular exposure scenario, an MOE of 200 was generated for representative exposure concentrations for an airline refueler; an MOE > 50 was generated for upper bound exposures. The potential for other aggregate exposures from multiple sources was not considered by the sponsor. Another possible exposure scenario of an occupationally exposed mother exposing her infant through ingestion of human milk was not considered by the sponsor because they contend that mothers exposed non-occupationally to urban air do not deliver a significant exposure to infants through human milk.

5.0. Summary of the Sponsor's Data Needs Assessment

The sponsor considers the most relevant route of exposure for the C_{10}-C_{12} n-alkanes to be the inhalation route. The sponsor considers the existing exposure data to be adequate to characterize the exposures that children and parents are likely to experience for this category of n-alkanes. The possible exposure scenario of an occupationally exposed mother exposing her infant through ingestion of human milk was not considered by the sponsor because they contend that mothers exposed non-occupationally to urban air do not deliver a significant exposure to infants through human milk. The sponsor acknowledges that possible data gaps exist on exposure, but contend that the low toxicity of the n-alkanes combined with the potential exposure scenarios yields large MOEs and therefore, further quantitative assessments of exposure were not justified.

The three n-alkanes were treated as a category by the sponsor. Furthermore, since the n-alkanes are not typically found in commerce as individual chemicals, but as commercial n-alkane streams or minor components of complex hydrocarbon fuel and solvent substances, data on representative commercial substances were included by the sponsor to further support the hazard characterization of the C_{10}-C_{12} n-alkane category and, where data for the individual n-alkane did not exist, the sponsor used data from other individual n-alkanes or commercial products as read-across to support the hazard characterization of the chemical. As a result, the sponsor contends that all Tier 1 toxicity studies have been conducted, as well as some Tier 2 studies including metabolism, in vivo genotoxicity, neurotoxicity, and carcinogenicity. While the sponsor has identified data gaps for Tiers 2 and 3 (two-generation reproductive toxicity, developmental neurotoxicity, and immunotoxicity), they were not considered data needs because the sponsor concluded that no indicators of specific concern for these endpoints were apparent from the existing database and, because many of these Tier 2 and 3 data gaps will be addressed by the testing of complex hydrocarbon mixtures, including the evaluation of jet and diesel fuel, under the U.S. HPV Challenge and OECD SIDS programs.

6.0. EPA Response to the Data Needs Assessment

The Tier 1 exposure assessment is complete but EPA notes that there are some transparency issues and unaddressed uncertainties. These are discussed below. However, EPA

does not believe that these areas would significantly impact the exposure estimates for the n-alkanes, and therefore characterizes these exposure areas as data gaps. Therefore, EPA does not recommend any Tier 2 exposure studies at this time for VCCEP.

EPA notes that the sponsor did not describe whether exposure frequency and duration were considered in addition to concentration when determining which exposure scenarios to further characterize in the assessment. EPA believes that this transparency issue is a data gap and would not have changed the conclusions regarding the need for a Tier 2 assessment.

EPA notes that the sponsor's discussion of environmental fate is oversimplified. This is noteworthy because the sponsor used the environmental fate discussion as partial support for the assessment's focus on inhalation exposure scenarios. The sponsor noted in the December 6, 2005 letter to the Agency that additional data on environmental fate and transport is being developed and will be provided to the Agency through the OECD SIDS program. The sponsor's submission did not discuss the Level I fugacity modeling and whether it supports the sponsor's claims regarding environmental persistence and partitioning. In addition, Level III fugacity modeling was not conducted and EPA notes that Level III fugacity modeling suggests that water, soil, and sediment are the major compartments for these chemicals when equal, continuous emissions to air, water, and soil occur. This is quite different from the results of the Level I fugacity modeling cited in the submission. EPA believes that this is a data gap and that the conclusions regarding the need for a Tier 2 assessment would not have changed had the sponsor improved the transparency and used the Level III fugacity modeling.

An NAS report on Jet Propulsion Fuel (JP-8), which contains approximately 28% of C_9-C_{14} n-alkanes, indicated that JP-8 may be "potentially toxic to the immune system, respiratory tract, and nervous system at exposure concentrations near the interim PEL of 350 mg/m^3." It recommends, among other things, additional toxicity testing and toxicokinetic studies, improved exposure analysis, and human biomonitoring for biomarkers for immunotoxicity. Based on the results of these studies, n-alkanes may need to be revisited.

For toxicity, the sponsor presented a case for considering decane, undecane, and dodecane as a single category and where data are lacking, using data on shorter and longer chain alkanes (alone or in mixtures) for comparative purposes. The sponsor did not include in the submission data on more complex chemical mixtures like hydrocarbon jet fuels because they contain non-alkane compounds thereby making direct comparisons of the n-alkanes with adverse effects impossible. EPA believes the rationale presented by the sponsor for both the category approach, and for the use of data from other individual n-alkanes or commercial products as read-across to fill in any data gaps to be a reasonable one.

The Tier 1 toxicity assessment is complete, and includes acute toxicity, mutagenicity, and two combined repeat-dose one-generation developmental/reproductive toxicity screening studies. In addition, several Tier 2 studies have been conducted including numerous repeat-dose toxicity studies, mutagenicity studies, and metabolism studies.

EPA has identified several data gaps for Tiers 2 and 3 toxicity studies (prenatal developmental toxicity studies in a second species, a two-generation reproductive toxicity study, chronic toxicity/carcinogenicity studies, neurotoxicity screening battery, and a developmental neurotoxicity study). However, the existing toxicity data base demonstrates a low concern for toxicity following exposure to n-alkanes; no clear, consistent target organs were identified, and the effects that were observed in the various toxicity studies are minimal and occurred at high doses/concentrations. It is unlikely that any new toxicity data would yield effects at levels substantially lower than the points of departure used in the current risk characterization such that it would be impacted in any significant way. Therefore, EPA does not recommend any additional Tier 2 or Tier 3 toxicity testing at this time for VCCEP. Statements of members of the Peer Consultation Panel support EPA's recommendations for VCCEP.

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EcoScale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters

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A novel post-synthesis analysis tool is presented which evaluates quality of the organic preparation based on yield, cost, safety, conditions and ease of workup/purification. The proposed approach is based on assigning a range of penalty points to these parameters. This semi-quantitative analysis can easily be modified by other synthetic chemists who may feel that some parameters should be assigned different relative penalty points. It is a powerful tool to compare several preparations of the same product based on safety, economical and ecological features.

Introduction

The acceptable preparation of an organic product involves not only a relatively efficient reaction but also the ease of workup and purification. Safety and ecological friendliness are also of paramount importance. Therefore, in order to evaluate the quality of the overall preparation process, it is important to examine all its components.

To address this issue, some partial metrics for the preparation efficiency have been developed. They are mainly used as a predictive tool for chemical processes on a larger scale when substituting a traditional chemical process with an alternative. [1,2] The main parameters and approaches are briefly discussed as follows.

Atom economy [3,4]

This parameter is the ratio of the molecular weight of the target molecule to the sum total of the molecular weights of all the substances produced in the stoichiometric equation for the reaction involved. It takes into account the amount of the reagents incorporated into the end product. Cycloadditions are examples of transformations with 100% atom economy. For other reactions (e.g. substitution reaction), a 100 % economy can never be reached due to the intrinsic nature of the reaction. The main use of this parameter is to adapt reaction sequences in a way that transformations with low atom economy are limited to a minimum.

Environmental factor (E-factor) [5-8]

This factor is the ratio of the weight of generated waste to the total weight of the end product. It is a useful tool for rapid evaluation of processes based on generated waste. For example, the comparison of E-factors of the homogeneous and heterogeneous catalytic processes in the alkylation of benzene shows a 30-fold preference towards the heterogeneous method. Recently, it has also been applied to assess the development of an environmentally benign synthesis of sildenafil citrate (Viagra™). [9] The E-factor for the final process is very low with just 6 Kg of waste per kilogram of product compared with an industry average of 25–100 Kg.

Environmental quotient (EQ) [10]

The value of the E-factor is limited as it does not take into account the nature and environmental impact of the generated waste. In order to arrive at a more meaningful prediction, the E-factor is multiplied by a environmentally hazardous quotient Q. For example, a Q value of 1 can be attributed to NaCl, while heavy metals can be assigned a value between 100–1000 on the basis of their toxicity. Based on the environmental quotient, a computer program has been developed (EATOS of Environmental Assessment Tool for Organic Synthesis) [11] that can be used to compare and improve chemical reactions.

Effective mass yield [12]

This parameter is defined as the percentage of the mass of desired product relative to the mass of all non-benign materials used in the synthesis. It introduces the important issue of (eco)toxicity.

Mass intensity [13]

The mass intensity is defined as the ratio of the total mass used in a process (step) and the mass of the end product. It takes into account the yield, stoichiometry, solvent, and the reagents used in synthesis. The total mass also includes chemicals (except water) used in workup procedures such as washes with acid, base, salt solution or organic solvent, as well as extractions and/or crystallizations.

Also, a few unified metrics has been developed which combine some of the above mentioned individual parameters and factors relevant for specific purposes.

The process profile [14]

Intended primarily as a management tool for economic evaluation, it takes into account all important factors involved in large scale production. These are process parameters, raw material cost, yield, throughput time, throughput volume, number of steps in synthetic sequence, special equipment requirements, reproducility, tolerance to abuse, linearity of sequence, environmental abuse potential, potential occupational health and safety hazards, raw material availability, susceptibility to regulatory changes and patent protection.

Life cycle analysis (LCA) [15,16]

In this methodology, all stages of the life cycle of a chemical as well as environmental impacts of by-products and auxiliaries (solvents, co-reagents, and technical facilities) are considered. It consists of three domains: the analysis of the starting material, the analysis of the impact, and the analysis of the improvements. It can be used to evaluate existing processes and/or design new processes.

Proprietary metrics

The above analyses often show that the cost of waste, including effluent treatment, waste disposal, loss of raw materials, etc., can amount up to 40% of the overall production costs. [17] This understanding has led to several governmental (e.g. Green Chemistry Program of the U.S. Environmental Protection Agency [18]) and corporate initiatives to develop their own set of qualitative and semiquantitative green parameters. For example, GlaxoSmithKline has published a set of metrics such as carbon efficiency (CE) and reaction mass efficiency (RME) which enables an assessment to be made of batch processes in terms of waste, energy usage, and chemistry efficiency. [19] These metrics are based on the number of chemistry steps, number of purification steps, number of isolated intermediates, total yield, nature of solvents, the use of extreme conditions, and the use of reagents with known environmental, safety or health problems, among others.

Unification of reaction metrics for green chemistry

The development of a new reaction metric, the stoichoimetric factor (SF), has been decribed which allows to take into account reactions run under nonstoichoimetric conditions. Based on four competing factors (reaction yield, atom economy, stoichoimetric factor and a factor accounting for reaction and postreaction solvent and/or catalyst recovery) a general algorithm for reaction mass efficiency has been proposed. [20] This has been followed by the introduction of minimum atom economy $(AE)_{min}$ and maximum environmental impact factor E_{max} that have been applied to over 400 named reactions. [21]

As can be seen from the discussion above, the search and implementation of the appropriate metrics for evaluation of the quality of a chemical process can be complex, time-consuming, not straightforward (unclear definitions) or too focused on one topic (waste, safety, etc.). In particular, the lack of transparency of the life cycle analysis, the lack of objectivity in assigning the Q value for a reagent or the unclear definition of "non-benign" for the calculation of effective mass yield, can be noted.

To our knowledge, no tool for evaluation of chemical reaction conditions on laboratory scale has been developed. Herewith, we propose a unified algorithm, called EcoScale, to help select an acceptable organic preparation.

Design of the EcoScale

Starting principles

A basic requirement for the design of the EcoScale is transparency and user-friendliness. At the same time, it needs to cover the whole range of organic chemistry conditions and techniques. To combine all these goals, the following approach is used.

First, the tool uses a scale from 0 to 100 with 0 representing a totally failed reaction (0% yield) and 100 representing the ideal reaction which is defined as follows: *Compound A (substrate) undergoes a reaction with (or in the presence of) inexpensive compound(s) B to give the desired compound C in 100% yield at room temperature with a minimal risk for the operator and a minimal impact for the environment.*

Table 1: The penalty points to calculate the EcoScale

Parameter	Penalty points
1. Yield	(100 – %yield)/2
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< $10)	0
Expensive (> $10 and < $50)	3
Very expensive (> $50)	5
3. Safety[a]	
N (dangerous for environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals[b]	1
Unconventional activation technique[c]	2
Pressure equipment, > 1 atm[d]	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3
5. Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	1
Heating, < 1 h	2
Heating, > 1 h	3
Cooling to 0°C	4
Cooling, < 0°C	5
6. Workup and purification	
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150°C	0
Crystallization and filtration	1
Removal of solvent with bp > 150°C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction[e]	3
Classical chromatography	10

[a]Based on the hazard warning symbols. [b] Dropping funnel, syringe pump, gas pressure regulator, etc. [c] Microwave irradiation, ultrasound or photochemical activation, etc. [d]$scCO_2$, high pressure hydrogenation equipment, etc. [e]If applicable, the process includes drying of solvent with desiccant and filtration of desiccant.

Secondly, 6 general parameters which influence the quality of reaction conditions are analyzed (Table 1). Within each of these parameters, individual penalty points of various relative weights are assigned that take into account all possible situations when setting up an organic chemistry experiment. The penalty points are cumulative for all components of the preparation. In order to simplify the EcoScale design, the usual differentiation between solvents (usually present in > 10 equiv.), reagents, auxiliary or co-reagents and catalysts (usually present in < 0.1 equiv) is not made.

Calculation of the EcoScale

An ideal reaction has the EcoScale value of 100. The EcoScale score for a particular preparation of the product in a high purity state (> 98%) is calculated by lowering the maximum value of 100 by any applicable penalty points.

EcoScale = 100 - sum of individual penalties

Discussion

Although the choice of these 6 parameters will likely reach consensus among organic chemists, their relative weight and the assignments of the actual value of the penalties can raise a discussion. Specifically, it must be stressed that the relative weights of these parameters in the decision process fundamentally differ when the scale of the reaction is considered. Basically, the focus shifts away from the overall time and convenience on a laboratory scale, to the overall cost in industry when all regulatory restrictions are considered. In particular, no restrictions for using specific reagents/solvents exist on a laboratory scale, but high yield reactions can still be banned for larger scale production; for example, by using a highly flammable or toxic solvent or an expensive reagent. Similarly, reactions at room temperature are far more important on an industrial scale as no energy is needed for heating or cooling. Also, the waste issue is of a minor importance at a laboratory scale but can take up a significant cost of a production process. Therefore, it is important to stress that this EcoScale is specifically designed for laboratory scale conditions.

Even with the scale issue in mind, each weight of the parameters and each (relative) value of the penalty points are often only based on experience and intuition and not on "exact science". The subjective basis of these values in EcoScale is explained in more detail below. In particular, the subjective assignment of particular weights to various penalty points can easily be modified, as some chemists may disagree with the proposed relative assignments. The EcoScale is designed to be a flexible tool.

1. Yield

The yield is one of the most important factors. Indirectly, this parameter includes selectivity issues, as the quality of a reaction increases with increasing the functional group compatibility. An independent selectivity parameter would make the analysis highly complicated. A high yield guarantees an optimal use of resources and usually results in an easy workup procedure as side-products are limited. The question remains which yield to take, before or after purification of the product? Theoretically, the pre-purification yield is the best but is not practical to implement. First, this yield is often not determined (and not mentioned in the literature). In addition, the value of reaction conditions from which the end product cannot efficiently be purified is questionable. Therefore, points are calculated for the isolated yield.

The EcoScale analysis can also be applied to the evaluation of non-racemic synthesis. In this case, only the chemical yield of the targeted enantiomer is considered. The use of efficient chiral auxilaries can significantly raise the EcoScale (higher yield of enantiomer), but the final score is strongly influenced by their amount, availability and safety profile.

2. Price of reaction components

Every reaction component is taken into account, and the penalties are cumulative. The categorization of the reaction components as "inexpensive/readily available" is subjective. We define a reaction component as inexpensive if the cost to use it to synthesize the end product on a 10 mmol scale does not exceed US$10 and very expensive when its price is over US$50. We realize that by using this criterion, the EcoScale is time dependent. A reaction component that is not commercially available today might appear in the catalogues next year and, as such, will rank higher on the EcoScale in the future. This is only fair because the evaluation process is also time dependent: we can refrain from using certain reagents today because we would need to synthesize them, but might use them in the future when they become commercially available.

Reaction components present in over 10 equivalents in the reaction mixture are usually solvents and often are inexpensive. However, common solvents used under strictly anhydrous and/or high-dilution (large volume) conditions should be re-evaluated as expensive components. The use of an expensive solvent (e.g. ionic liquid) does not necessarily mean a lower score on the EcoScale, as a higher yield, a better safety profile or easier workup can favourably balance the score. In addition, two special cases can be noted. In a solvent-free reaction and when the solvent is used as the reagent, there is one reaction component less for which no extra penalties are deducted. It must be noted that the physicochemical characteristics are not taken into account here: solvents with a boiling point higher than 150 °C (DMF, DMSO, diglyme, DMA, HMPTA etc.) and lower than 25 °C (e.g. $scCO_2$) are penalized but in a different category (workup and technical setup, respectively).

Similarly, the price of reaction components present in a small amount (usually catalysts) is determined by the mol% needed. An expensive but efficient catalyst (e.g. with high turnover number, low mol% needed) can qualify as an inexpensive component. The same catalyst can have a price penalty if used in another reaction in 10 mol% ratio. It must be stressed that the real benefits of using catalysts usually are reflected in higher selectivity (yield) and lower energy requirements, which are accounted for in other parts of the EcoScale.

3. Safety

Safety is of paramount importance when carrying out organic chemistry experiments. Working with chemicals is never without a risk, and it is necessary to fully understand any potential hazard. Organic compounds can be carcinogenic, mutagenic, teratogenic, corrosive, lachrymatic, highly flammable or explosive, among other things. In addition, the hazard can increase over time, and photooxidation of ether to generate explosive peroxides is a good example. It must also be emphasised that it takes a long time before the safety profiles of new products are fully characterized. Finally, one should never forget that the combination of certain individual compounds can create a hazardous situation (e.g. exothermic reaction between acids and bases).

For assessing these hazards, a wide variety of information is readily available, such as the health and safety information in Risk/Safety phrases, the Material Safety Data Sheets, and the hazard warning symbols on the containers. In order to avoid a complex calculation, the hazard warning symbols are taken as a reference. In particular, each reaction component labelled with T+ (extremely toxic), F+ (extremely flammable) or E (explosive) is penalized with 10 points while reaction components labelled with T (toxic), F (highly flammable) or N (dangerous to the environment) are given 5 penalty points. [22] As can be seen from Table 1, the use of unsafe compounds can downgrade the overall quality of synthesis to the greatest extent in comparison to other entries.

4. Technical setup

A simple setup consisting of a regular flask, reflux condenser, and stirrer receives no penalty points. Any extras including special glassware, equipment for controlled addition of chemicals, pressurized vessels, the application of unconventional techniques such as microwave irradiation, ultrasound or photochemistry, and the need for an

Table 2: The penalty points for example 1

# 1–6 from Table 1	Penalty
1 Yield: 90 %	5
2 5% Pt/C, 0.3 g	3
3 Nitrobenzene (T, N)	10
MeOH (T, F)	10
5% Pt/C (F)	5
4 Common glassware, stirring	0
5 Room temperature, 1 h	0
6 Filtration of the catalyst	0
Removal of MeOH	0
Addition of $CHCl_3$	0
Washing with aq. NaCl	3
Removal of $CHCl_3$	0
Penalty points total:	36

inert atmosphere, especially in a glove box, downgrade the overall quality of the synthesis.

5. Temperature/time

The reaction temperature and time are closely related. In an ideal situation, a reaction proceeds rapidly at room temperature. However, heating is often required to accomplish synthesis in an acceptable period of time. On the other hand, cooling is more difficult than heating. Above room temperature, the heating range is continuous while for cooling in a conventional way (without the use of a cryostat) only fixed temperatures (e.g. 0°C for ice bath or -78°C for acetone/sCO_2) are available, and great care must be taken sometimes to avoid moisture in order to produce reproducible results. These features are reflected in the relative penalty points. The penalties are cumulative; if heating and cooling are required during the reaction, both must be accounted for.

6. Workup and purification

The workup and purification of the end product can be a tedious process. In order to avoid a complex calculation (e.g. when taking into account all used chemicals), the factor "a period of time to obtain the end product in a purity of over 98%" is taken as the main criterion in assigning the points. As it makes no sense to use a chronometer in a laboratory workup procedure, standard purification techniques are ranked according to their execution time (and convenience). Every workup step is taken into account in assigning the penalty points.

Ranking of reaction conditions

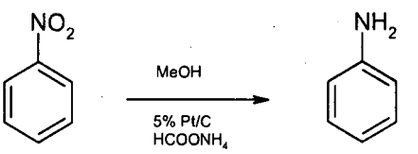
The reaction conditions used in the preparation of a high purity (> 98%) product is ranked on a scale from 0 to 100 using the following scores: > 75, excellent; > 50, acceptable; and < 50, inadequate.

Table 3: The penalty points for example 2

# 1–6 from Table 1	Penalty
1 Yield: 87%	6
2 H_2O_2 (30%, 4.1 mL, 36 mmol)	0
$Na_2WO_4 \cdot 2H_2O$ (66 mg, 0.2 mmol)	0
$[(Octyl)_3NMe]HSO_4$ (93 mg, 0.2 mmol)	0
Molecular sieves 4Å (100 mg)	0
3 Benzyl chloride (T)	5
4 Dropwise addition of H_2O_2	1
5 90°C, 10 h	3
6 Extraction with AcOEt (3 × 10 mL)	3
Washing with aq. $Na_2S_2O_4$	3
Drying over $MgSO_4$	0
Removal of AcOEt	0
Crystallization from hexanes	1
Penalty points total:	22

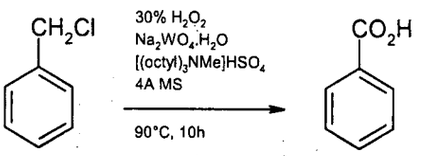
Examples of calculations

The EcoScale evaluations of four important synthetic transformations taken from the recent literature are shown below. Workup involves manipulations in the given order.



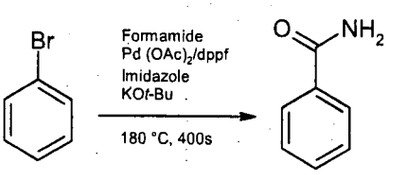
Scheme 1: Reduction of nitrobenzene to aniline [23]

The sum of all penalty points is 36 (Table 2), which gives total score of 64 on the EcoScale (an acceptable synthesis).



Scheme 2: Oxidation of benzyl chloride to benzoic acid [24]

The sum of all penalty points is 22 (Table 3), which gives total score of 78 on the EcoScale (an excellent synthesis).



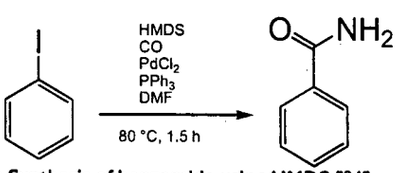
Scheme 3: Synthesis of benzamide [25]

The sum of all penalty points is 47 (Table 3), which gives total score of 53 on the EcoScale (an acceptable synthesis).

Table 4: The penalty points for example 3

# 1–6 from Table 1	Penalty
1 Yield: 83%	9
2 Formamide (1 mL)	0
$Pd(OAc)_2$ (0.038 mmol, 8.5 mg)	0
dppf (0.038 mmol, 21.1 mg)	0
Imidazole (0.75 mmol. 51.1 mg)	0
KOBu-*t* (1.13 mmol, 126 mg)	0
3 Bromobenzene (N)	5
Formamide (T)	5
KOBu-*t* (F)	5
dppf (T)	5
4 Microwave activation	2
Nitrogen atmosphere	1
5 180°C, 400 s	2
6 Cooling	0
Dilution with EtOAc	0
Washing with water and brine	3
Drying over potassium carbonate	0
Removal of EtOAc	0
Silica gel chromatography	10
Penalty points total:	47

In the introduction to the article, [25] the authors claim that this procedure for preparing primary amides starting from aryl halides is better than another procedure which uses hexamethyldisilazane (HMDS). [26] Therefore, the EcoScale for the latter procedure was also calculated to compare the two preparations.



Scheme 4: Synthesis of benzamide using HMDS [26]

The sum of all penalty points is 68 (Table 4), which gives total score of 32 on the EcoScale (an inadequate synthesis).

This procedure receives a significantly lower score than the previous example largely due to its safety profile and the more tedious workup. By using EcoScale, the two analyses (#3 and #4) illustrate a rapid selection of the better preparation (#3).

Conclusion

In general, the EcoScale favours high-yielding, low-cost and safe reaction conditions and an easy purification. The analysis (1) is straightforward (it takes into account all important parameters), (2) is transparent (it is clear how the final score is obtained), (3) is fast (it can be calculated in less than 5 min) [27], (4) does not take a general standpoint but takes into account advantages and disadvantages of specific methodologies or auxiliary reagents, (5) offers a general overview of the reaction conditions, and the areas for improvement are clearly indicated. In this way, it can be used as a convenient tool in education (students learn to analyze a reaction protocol), and is valuable in research as an effective way to compare different sets of preparations of the same product.

Table 5: The penalty points for example 4

# 1–6 from Table 1	Penalty
1 Yield: 76%	12
2 HMDS (4 equiv.)	0
CO (in excess)	0
$PdCl_2$ (0.03 equiv.)	0
PPh_3 (0.06 equiv.)	0
DMF	0
3 CO (T, F+)	15
HMDS (F)	5
DMF (T)	5
PPh_3 (N)	5
Bromobenzene (N)	5
4 Controlled addition	1
CO atmosphere	1
5 80°C, 1.5 h	3
6 Cooling	0
Addition MeOH	0
Addition 2N H_2SO_4	0
Extraction with AcOEt	3
Washing with aq.$NaHCO_3$ and brine	3
Silica gel chromatography	10
Penalty points total:	68

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