Formulating With Safer Alkanolamine Options

06 July 2016, Wednesday
Innovation Seminar Theatre
Dr. Yeo Kim Long
Overview

- Introduction to ANGUS
- Nitrosamines
- Formation of nitrosamines
- Nitrosamines are harmful
- The ANGUS Solution
### Legacy of Making the Best Better

- The world’s only company dedicated to nitroalkanes and their derivatives
- Unique production expertise spanning over 70 years
- Extensive track record of industry innovation and leadership
- Solutions-driven, multifunctional additives for a broad range of applications and markets
- Regional Customer Application Centers to address the local needs of our customers
- Strong focus on Responsible Care® and product stewardship

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1928</td>
<td>Purdue University chemist Henry B. Hass begins nitroalkanes research</td>
</tr>
<tr>
<td>1934</td>
<td>First nitroalkane patent granted</td>
</tr>
<tr>
<td>1935</td>
<td>Commercial Solvents Corporation (CSC) enters licensing agreement with Purdue University</td>
</tr>
<tr>
<td>1940</td>
<td>CSC begins commercial nitroalkane production</td>
</tr>
<tr>
<td>1975</td>
<td>International Minerals and Chemical Corporation (IMC) purchases CSC and creates separate nitroalkanes division</td>
</tr>
<tr>
<td>1982</td>
<td>Alberta Natural Gas buys nitroalkanes business, forming ANGUS Chemical Company</td>
</tr>
<tr>
<td>1999</td>
<td>Dow Chemical purchases ANGUS</td>
</tr>
<tr>
<td>2014</td>
<td>ANGUS AMP® granted VOC-exempt status</td>
</tr>
<tr>
<td>2015</td>
<td>Golden Gate Capital (GGC) investment group seeks to unleash the growth potential of ANGUS</td>
</tr>
</tbody>
</table>
ANGUS is the only manufacturer in the world that uses propane nitration technology to create a unique set of products.

Propane

Nitration of propane yields our nitroalkane products

Nitroalkanes (Nitromethane, Nitroethane)

Nitroalcohols are formed via the reaction of nitroalkanes and aldehydes

Nitroalcohols

Aminoalcohols (AMP®, TRIS AMINO®) are formed via the reduction of nitroalcohols

Aminoalcohol Derivatives (ZOLDINE®, ALKATERGE®) are converted to derivatives via reactions with aldehydes or carboxylic acids

Technology innovator with over 70 years of nitration expertise
Key Market Focus

Personal Care

Life Sciences

Industrial Specialties

ANGUS is focused and aligned to drive innovation, enabling ANGUS and our customers to deliver sustainable growth.
Nitrosamine

\[ \text{R} - \overset{\cdot}{\text{N}} - \overset{\cdot}{\text{O}} \quad \text{and} \quad \text{R} - \overset{\cdot}{\text{N}} - \overset{\cdot}{\text{H}} \]
Nitrosamines – What is it?

- Can be converted from primary, secondary and tertiary amines by nitrosating agents under physiological conditions

- Secondary and tertiary amines form very stable nitrosamines
Nitrosamines – What is it?

- Presence of an α-hydrogen permits formation of a very stable carcinogenic nitrosamine

Tromethamine
CAS 77-86-1

Triethanolamine
CAS 102-71-6
# Common Carcinogenic Nitrosamines

<table>
<thead>
<tr>
<th>Nitrosamine</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-nitrosodiethanolamine (NDELA)</td>
<td>DEA/TEA</td>
</tr>
<tr>
<td>N-nitrosobis (2-hydroxypropyl)amine (NBHPA)</td>
<td>BHPA</td>
</tr>
<tr>
<td>N-nitrosodiisopropanolamine</td>
<td>DIPA</td>
</tr>
<tr>
<td>N-nitrosomorpholine</td>
<td>Morpholine</td>
</tr>
<tr>
<td>N-nitrosomethylstearylamine</td>
<td>Dimethylstearylamine</td>
</tr>
</tbody>
</table>
Nitrosamine Formation
Common Nitrosating Agents:

<table>
<thead>
<tr>
<th>Species</th>
<th>Acidic medium</th>
<th>Neutral medium</th>
<th>Slightly basic medium (pH = 7.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{H}_2\text{ONO}^+$</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{NO}^+$</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>$\ast\text{YNO}$</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>$\text{HNO}_2$</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>$\text{N}_2\text{O}_3$</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

$\ast Y$ is a non-basic nucleophile. It can be neutral as well.

Nitrite (NO$_2^-$) and nitrous acid (HNO$_2$) are the primary precursors of nitrosating agents.
Overview of Generating Nitrosating Agents

\[
\begin{align*}
H_2ONO^+ & \xrightarrow{-H^+} HONO & \xrightarrow{-H_2O} HNO_2 & \xrightarrow{+H^+} HNO_2^+ \\
\downarrow & \downarrow & \downarrow & \downarrow \\
Y^- & \xrightarrow{+Y} YNO & \xrightarrow{-OH^-} NO_2^- & \xrightarrow{+O_2} NO_3^- \\
\downarrow & \downarrow & \downarrow & \downarrow \\
YNO + H_2O & \xrightarrow{-H} HNO_2 & \xrightarrow{-NO_2^-} NO_2 & \xrightarrow{-NO} NO + NO_2 \\
\end{align*}
\]

Active nitrosating agents are underlined

Generation of $\text{N}_2\text{O}_3$

$\text{NO}_x$
(from the environment)

$\rightarrow$

$\text{HNO}_2$

$\rightarrow$

$\text{NO}_2^-$

$\text{NO/NO}_2$

$2 \text{NO}_2 + 2 \text{H}_2\text{O} \rightarrow 2 \text{HNO}_2 + \text{H}_2\text{O}$

$\text{NO} + \text{NO}_2 + \text{H}_2\text{O} \rightarrow 2 \text{HNO}_2$

Hydrolysis of $\text{NO}_x$

$\text{HNO}_2 \rightarrow \text{H}^+ + \text{NO}_2^-$
Generation of N$_2$O$_3$

In neutral or alkaline environment, NO$_x$ forms nitrites

\[
\begin{align*}
\text{N}=\text{O} & \quad \text{+ H}^+ \quad \leftrightarrow \quad \text{HO-N}=\text{O} \\
\text{N} & \quad \text{OH} \quad \leftrightarrow \quad \text{H} \quad \text{NO} \quad \text{OH} \\
\text{H} & \quad \text{N} \quad \text{O} \quad \leftrightarrow \quad \text{HO-N}=\text{O} \\
\end{align*}
\]

Sources of NO$_x$

Industrial

Transportation

Agriculture
Secondary Amine Nitrosation

Most reactive to nitrosation out of the different classes of amines

Tertiary Amine Nitrosation

Tertiary amine converts to a secondary amine that will follow the same nitrosation pathway of secondary amine.


Primary Amine Nitrosation

Attacks N instead of O. O is more electronegative; hence the electron density of the triple bond will be more attracted to O than N. This makes N more electron deficient → more prone to nucleophilic attack by amine.

Will be converted into Nitrogen, Alcohols and Alkenes in the presence of nucleophile.
Secondary and Tertiary amines Convert into Stable Nitrosamines
Why Should We Be Concerned?
Nitrosamines are Harmful
Why should we be concerned?

- 80-90% of N-nitroso compounds are carcinogenic\textsuperscript{1,2}
- Environmental level exposure may lead to the formation of malignant tumors (cancer).

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Agency for Research on Cancer (IARC)</td>
<td>Group 2A – Probably carcinogenic to humans</td>
</tr>
<tr>
<td>European Union (EU)</td>
<td>Category 2 - Presumed to have carcinogenic potential for humans largely based on animals evidence</td>
</tr>
<tr>
<td>Environmental Protection Agency (EPA)</td>
<td>Likely to be carcinogenic to humans</td>
</tr>
</tbody>
</table>

\textsuperscript{1} 2012. Nitrosation of volatile amines at the workplace [MAK Value Documentation, 1990]. The MAK Collection for Occupational Health and Safety. 24–37
Nitrosamines May Cause Cancer
Cancer Formation Overview

• DNA mutation
• Mutant protein formation
• Cell cycle dysregulation
• Uncontrolled cell division and growth

http://www.nature.com/onc/journal/v30/n32/fig_tab/onc2011160f3.html
The Central Dogma

- Fidelity of DNA and RNA critical to ensure correct amino acid added during protein synthesis

http://legacy.owensboro.kctcs.edu/gcaplan/lab/notes/LAB%20notes%20DNA.htm
Point Mutation Due to Nitrosamines

- Formation of diazonium cation from nitrosamine via Cyt P450
- O(6)-methylation of guanine (G)
- O(6)-methylguanine (O6-meG) preferentially pairs with thymidine (T) instead of cytidine (C)

Preferred: O6-meG-T
Non-preferred: O6-meG-C

http://www.atdbio.com/content/15/Mutagenesis-and-DNA-repair
Point Mutation Due to Nitrosamines

- meG – A base pair mismatch results in propagation of genetic code error

G T T
C A A

mG T T
C A A

mG T T
T A A

A T T
T A A

O(6)-methylation of guanine

Unstable mG – C base pairing

During DNA replication, mG forms more stable base pair with T

* If error uncorrected

Complementary strand will be replicated as ATT

Genetic code is now TAA instead of CAA

T instead of C is added
Cancer Formation

- Base pair mismatch results in wrong message

DNA

<table>
<thead>
<tr>
<th>G T T</th>
<th>C A A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>O(6)-methylation</td>
<td></td>
</tr>
</tbody>
</table>

RNA

<table>
<thead>
<tr>
<th>mG T T</th>
</tr>
</thead>
<tbody>
<tr>
<td>C A A</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Replication</td>
</tr>
</tbody>
</table>

Amino acid

<table>
<thead>
<tr>
<th>mG T T</th>
</tr>
</thead>
<tbody>
<tr>
<td>* If error uncorrected</td>
</tr>
<tr>
<td>T A A</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Replication</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>A T T</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAA</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>STOP</td>
</tr>
</tbody>
</table>

O(6)-methylation

http://sitn.hms.harvard.edu/flash/2011/issue97/
Cancer Formation

- Base pair mismatch results in malformed proteins

**DNA**

\[ \text{GTT} \]
\[ \text{CAA} \]

**RNA**

\[ \text{mGTT} \]
\[ \text{CAA} \]

**Amino acid**

\[ \rightarrow \text{C A A} \]

\[ \rightarrow \text{Glycine} \]

*If error uncorrected*

\[ \text{mGTT} \]
\[ \text{CAA} \]
\[ \rightarrow \text{UAA} \]
\[ \rightarrow \text{STOP} \]

A 38 amino acid protein may become a 30 amino acid mutant protein

→ Mutant protein cannot function properly
Nitrosamines May Cause Cancer

- Secondary amines like DEA, and tertiary amines like TEA, can be easily converted into stable nitrosamines
- Cytochrome P450 in the body converts nitrosamines into diazonium ions
- Diazonium ions cause O(6)-methylation of guanine
- O(6)-methylated guanine mismatches with thymidine instead of cytidine
Nitrosamines May Cause Cancer

- Nonsense mutation can result in the formation of mutant protein
- Mutant protein can be critical to cell cycle control
- Uncontrolled cell division

http://www.examiner.com
The ANGUS Solution
ANGUS ULTRA PC™
Primary Amines

• Primary Amine Functionality

AMP-ULTRA™ PC
INCI: aminomethyl propanol
CAS: 124-68-5
EiNECS: 204-709-8

AMPD™ ULTRA PC
INCI: aminomethyl propanediol
CAS: 115-69-5
EiNECS: 204-100-7

TRIS AMINO™ ULTRA PC
INCI: Tromethamine
CAS: 77-86-1
EiNECS: 201-064-4

• No α-hydrogen
Globally-compliant

- Brazil ANVISA Mercosur Resolution on Cosmetics and Personal Care Products
- The Ministry of Health (MOH) of the People’s Republic of China Hygienic Standards for Cosmetics (2007 version)
- KOREA: A KFDA revision of the regulations on cosmetic raw materials (2010-99)
  - Minimum Purity 99%
  - Maximum secondary amine content 0.5%
  - Maximum nitrosamine content 50 µg/kg (ppb)
  - Must store in nitrite-free containers
Globally Compliant

- REACH-registered
- Compliant with global chemical control inventories

✓ USA - TSCA
✓ Canada - DSL
✓ EU - EINECS
✓ China - IECSC
✓ Taiwan
✓ Japan - ENCS
✓ Korea - KECI
✓ Philippines - PICCS
✓ Australia - AICS
✓ New Zealand - NZIOC
## Globally Compliant and High Purity

<table>
<thead>
<tr>
<th>Product</th>
<th>pKa</th>
<th>Mw</th>
<th>Appearance</th>
<th>FP/MP, °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMP-ULTRA™ PC 1000 INCI: aminomethyl propanol</td>
<td>9.72</td>
<td>89</td>
<td>Anhydrous solid</td>
<td>30</td>
</tr>
<tr>
<td>AMP-ULTRA™ PC 2000 INCI: aminomethyl propanol</td>
<td>9.72</td>
<td>89</td>
<td>Low viscosity liquid (5% water)</td>
<td>13</td>
</tr>
<tr>
<td>AMP-ULTRA™ PC 3000 INCI: aminomethyl propanol</td>
<td>9.72</td>
<td>89</td>
<td>Low viscosity liquid (11% water)</td>
<td>-3</td>
</tr>
<tr>
<td>AMPD™ ULTRA PC INCI: aminomethyl propanediol</td>
<td>8.76</td>
<td>105</td>
<td>Crystalline solid</td>
<td>100</td>
</tr>
<tr>
<td>TRIS AMINO™ ULTRA PC INCI: tromethamine</td>
<td>8.03</td>
<td>121</td>
<td>Crystalline solid</td>
<td>165</td>
</tr>
</tbody>
</table>
Global Reach, Local Focus
Conclusion

• Secondary and tertiary amines may convert into stable nitrosamine

• Nitrosamines may induce nonsense mutations in the genome, resulting in mutant proteins

• Mutant proteins may induce cancer formation

• ANGUS ULTRA PC™ range of primary amines are globally compliant solutions to avoid nitrosamine formation in formulated personal care products

• ANGUS provides global support for your formulating needs
WE MAKE THE BEST PERFORM BETTER.
Thank You. Questions?