Natural N-Acetyl Glucosamine

Joint Health
Global Company established in southern Japan
For 40 years in Europe and over 60 in Japan and USA
Involved in High Technology
More than 800 people dedicated to R&D (over 10% staff)
Social responsibility

Science FOR the People

Quality Of Life Division is developing and producing INNOVATIVE and NATURAL ACTIVE ingredients, in southern Japan and in the USA, to answer your needs
KANEKA offers the unique manufacturing method of Natural N-Acetylglucosamine through Enzymatic Hydrolysis.

Nature offers N-acetylglucosamine and naturally human body uses it everywhere.

The synovial viscous fluid is reducing friction between joint cartilage of synovial joints during movement and contains 3-4mg/mL hyaluronic acid.
N-Acetyl Glucosamine (one of the 8 essential human aminosugars) is key building block of main component (HA) of synovial fluid.

N-Acetyl Glucosamine and Glucosamin stimulate the biosynthesis of the glycosaminoglycans (GAG) needed for the formation of cartilage, bone, ligaments, tendons, sclera, and other specialized connective tissues.

(NAG is further along the pathway for GAG formation than Glucosamin!)
Natural N-acetylglucosamine

- Substrate for GAG synthesis
- Activator of GAG synthesis
- Inhibitor of degradation of connective tissues of the joints
- Antioxidant that traps damaging reactive oxygen species
- Anti-inflammatory
- Stimulator of synthesis of other components such as hyaluronic acid
- EINECS/ELINCS n°: 233-115-1
- Natural N-acetylglucosamine
- GRAS status
- White crystalline powder
- High purity >95%
- Sweet taste (half of sucrose)
- High water-soluble (21.8% w/w at Room Temp.)
- More Stable than glucosamine
  - Against pH change
  - Against heating
- Better bioavailability about 3 times of glucosamine
- Effective dose 500 mg/day vs 1 500 mg glucosamine/day
Stability of Kaneka™ vs. glucosamine against heating (Maillard reaction) and pH (5% solution)

Before Heating

100°C, 1 hr

121°C, 15 min
Bioavailability of N-Acetyl Glucosamine

Blood Concentration of Radioactivity after a Single Oral Administration of N-Acetyl-D-[1-14C] Glucosamine to Rats. (Dose:250mg/kg)

Distribution NAG vs Glucosamine (14C) according 2 studies

- **Bioavailability of NAG is about 3 times of glucosamine sulfate**
- **Moreover Glucosamine has to be converted to NAG: the key source of polyglycans**

Joint Health functions of Kaneka NAG

- Enhance of production of hyaluronic acid

- Healing of damaged cartilage

- NAG as inhibitor of inflammatory processes
  Shikmann et al, The Journal of Immunology, 2001, 166:5155-5160

- “Enhanced healing of cartilaginous injuries by NAG.”
  Tamai et al, Carbohydrate Polymers 54 (2003), 251-262
Hyaluronic acid in the skin decreases with aging

It is important to maintain HA content highly in skin in order to keep youth of the skin

### Bioavailability - Kaneka NAG vs hyaluronic acid

<table>
<thead>
<tr>
<th>Sample conc. (µg/ml)</th>
<th>Concentrations of Kaneka NAG / HA in the fluid (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>HA</td>
</tr>
<tr>
<td>500</td>
<td>HA</td>
</tr>
<tr>
<td>100</td>
<td>HA</td>
</tr>
<tr>
<td>150</td>
<td>HA</td>
</tr>
<tr>
<td>200</td>
<td>HA</td>
</tr>
</tbody>
</table>

*(Everted sac method (Internal data)*

![Graph showing concentrations of Kaneka NAG / HA over time](image.png)
Kaneka NAG™ increases the content of hyaluronic acid in skin

The content of hyaluronic acid in skin of hairless rats fed with NAG for a month.

![Bar graph showing the content of hyaluronic acid in skin (µg/dry tissue) for different NAG doses and skin layers.](image)
Clinical effect of Kaneka NAG on osteoarthritis

Method
Subject: osteoarthritis patient (n=31)
(Age: 74.4 ± 8.3)
Dose: Beverage containing
• at 0mg (Placebo)
• at 500mg
• at 1,000mg
  for 8 weeks daily oral intake

Analysis: Clinical diagnostic score
Doctor judge the result using “Criteria for outcome from the therapy of osteoarthritis” which established by The Japanese Orthopaedic Association.

This score is calculated by Pain, ability of walking and going up and down stairs, bending angle of knee, swelling, wellness etc.

Enhanced healing of cartilaginous injuries by Kaneka NAG

1 g/day

Two weeks

KANEKA NAG

Anti-inflammatory activity

## Summary of Safety Data of natural Kaneka NAG

<table>
<thead>
<tr>
<th>Study type</th>
<th>Species/Test system</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-clinical study</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acute toxicity</td>
<td>Rat single oral administration</td>
<td>The median lethal dose (LD₅₀) : &gt; 5,000 mg/kg.</td>
<td>Report of Biosafety research center, food, drug and pesticides. March, 6, 1991.</td>
</tr>
<tr>
<td>90-day subchronic toxicity</td>
<td>Rat 90 days repeated dose study</td>
<td>no-observed-adverse-effect level (NOAEL) : 2,476mg/kg/day (male) 2,834mg/kg/day (female)</td>
<td>Food Chem Toxicol. 42(4), 687-695, 2004.</td>
</tr>
<tr>
<td><strong>Clinical studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-weeks repeated dose study</td>
<td>Human (aged subject with osteoarthritis (average age: 74.4 years old)) 500, 1000 mg/man Oral administration</td>
<td>No side effect was observed</td>
<td>J New Rem &amp; Clin, 52, 301-312, 2003.</td>
</tr>
</tbody>
</table>