May neonicotinoid insecticides cause neurodevelopmental disorder by environmental exposure?

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Today’s message

• Neurodevelopmental Disorders may be caused by not only genetic factors, but also environmental chemicals, such as air pollutant, metal, and pesticides.

• Neonicotinoid insecticides (neonics) are world best selling systemic pesticides, nicotinic acetylcholine receptor agonist.

• **Neonics might cause neurodevelopmental disorders by environmental exposure**, because in vitro, animal, and clinical studies suggest it, recently.

• We have few evidence that neurodevelopmental disorders are not increasing by use of neonicotinoids.

• To keep natural child neurodevelopment, to revise acceptable dose of intake of neonicotinoids are one of the rational ways.

• I have no COI with regard to our presentation.
Children (6-14 years old) with special need by neurodevelopmental disorders in Japan

- Consistently increasing in these ten years (Ministry of Education, Culture, Sports, Science and Technology, 2015).
EPA also observe the same phenomena in 2015

- **Attention-Deficit/Hyperactivity Disorder (ADHD)**
  - Percentage of children ages 5 to 17 years reported to have ADHD, by sex, 1997-2013
  - Data characterization: Data for this indicator are obtained from an ongoing annual survey conducted by the National Center for Health Statistics.
  - Survey data are representative of the U.S. civilian noninstitutionalized population.
  - A parent or other knowledgeable adult in each sampled household is asked questions regarding the child’s health status, including if they have ever been told the child has ADHD.

- **Autism**
  - Percentage of children ages 5 to 17 years reported to have autism, 1997-2013
  - Data characterization: Data for this indicator are obtained from an ongoing annual survey conducted by the National Center for Health Statistics.
  - Survey data are representative of the U.S. civilian noninstitutionalized population.
  - A parent or other knowledgeable adult in each sampled household is asked questions regarding the child’s health status, including if they have ever been told the child has autism.

- **Learning Disability**
  - Percentage of children ages 5 to 17 years reported to have a learning disability, by sex, 1997-2013
  - Data characterization: Data for this indicator are obtained from an ongoing annual survey conducted by the National Center for Health Statistics.
  - Survey data are representative of the U.S. civilian noninstitutionalized population.
  - A parent or other knowledgeable adult in each sampled household is asked questions regarding the child’s health status, including if they have ever been told the child has a learning disability.

- **Intellectual Disability (Mental Retardation)**
  - Percentage of children ages 5 to 17 years reported to have intellectual disability (mental retardation), 1997-2013
  - Data characterization: Data for this indicator are obtained from an ongoing annual survey conducted by the National Center for Health Statistics.
  - Survey data are representative of the U.S. civilian noninstitutionalized population.
  - A parent or other knowledgeable adult in each sampled household is asked questions regarding the child’s health status, including if they have ever been told the child has mental retardation. Starting in 2011, the term “mental retardation” in the question was revised to “an intellectual disability, otherwise known as mental retardation.”

From 1997 to 2013, the proportion of children ages 5 to 17 years reported to have ever been diagnosed with ADHD increased from 6.3% in 1997 to 10.7% in 2012 and 9.9% in 2013.

In 2013, 8.2% of children ages 5 to 17 years had ever been diagnosed with a learning disability. There was little change in this percentage between 1997 and 2013.

For the years 2010–2013, the percentage of boys reported to have a learning disability (10.4%) was higher than for girls (6.6%). This difference was statistically significant. (See Table H7a.)

The percentage of children ages 5 to 17 years reported to have ever been diagnosed with autism rose from 0.1% in 1997 to 1.2% in 2013. This increasing trend was statistically significant.

In 2013, 1.4% of children ages 5 to 17 years were reported to have ever been diagnosed with intellectual disability (mental retardation). This percentage fluctuated between 0.6% and 0.9% from 1997 to 2010, and was between 1.3% and 1.4% from 2011 to 2013.

*The estimate should be interpreted with caution because the standard error of the estimate is relatively large: the relative standard error, RSE, is at least 30% but is less than 40% (RSE = standard error divided by the estimate).*
The cause of neurodevelopmental disorders (EPA 2015)

• **Attention-Deficit/Hyperactivity Disorder (ADHD)**
  - Genetic factor
  - Maternal smoking during pregnancy
  - Preterm birth, Low birth weight, Psychosocial adversity
  - Lead, PCB, Phthalate, *Organophosphate pesticides*, Perfluorinated chemicals, Mercury

• **Learning disability**
  - Genetic factor
  - Problem during pregnancy
  - Lead, Tabacco Smoke, Mercury, PCB

• **Autism Spectrum Disorders**
  - Genetic factor
  - *Pesticide*, Mercury, Air Pollutant, Phthalates

• **Intellectual Disability (Mental Retardation)**
  - genetic disorders, traumatic injuries, and prenatal events
  - Lead, mercury, PCB, *organophosphate pesticides*, PBDEs, phthalates, PAHs
Neurodevelopmental Disorders may be caused by pesticides

- **Insecticides are neurotoxic.**

- **Several epidemiological study showed positive relationships between environmental pesticide exposure and neurodevelopmental disorders.**

- **However, the data about neonicotinoids are rare.**

<table>
<thead>
<tr>
<th>Neuronal effect site</th>
<th>ADHD</th>
<th>autism</th>
<th>Developmental delay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organochlorines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na+ channel</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Organophosphates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzyme</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Pyrethroids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na+ channel</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Neonicotinoids</strong></td>
<td></td>
<td></td>
<td>?</td>
</tr>
</tbody>
</table>
Neonicotinoids are systemic insecticides.  
- Long lasting in plant, famous as honey bee’s risk.  
- Nicotinic acetylcholine receptor (nAChR) agonists

<table>
<thead>
<tr>
<th>Halogenated</th>
<th>Chlorinated (organochlorine)</th>
<th>Fluorinated</th>
<th>Non-halogenated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloropyridyl</td>
<td>Chlorothiazolyl</td>
<td>Sulfoximine</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>Imidacloprid</td>
<td>Acetamiprid</td>
<td>Sulfoxaflor</td>
<td>Dinotefuran</td>
</tr>
<tr>
<td>Nitenpyram</td>
<td>Thiacloprid</td>
<td>F₃C-</td>
<td></td>
</tr>
<tr>
<td>Clothianidin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloxaprid</td>
<td>Flupyradifurone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Shipment of neonicotinoids (tons)

CA=424,000 km²

JAPAN=378,000 km²

Nitempyram
Thiamethoxam
Thiacloprid
Imidacloprid
Dinotefuran
Clothianidin
Acetamiprid

STATE OF CALIFORNIA PESTICIDES SOLD IN CALIFORNIA FOR YEAR: 1996-2014

Database of National Institute for Environmental Studies: 1993-2014
nAChRs have critical role in neurodevelopment.

- In the human fetal cerebellum, α4, α7, β2, and β4 nAChRs are highly expressed (Hellström-Lindahl, 1998).
- Endogenous cholinergic signaling via nAChRs is important in determining the morphological and functional maturation of neural circuit formation (Miwa, 2011).
- Glutamatergic synapse formation is promoted by α7-containing nAChRs and affected by nicotine exposure in hippocampal and cortical neurons (Lozada, 2012).
- Retinal β2 nAChRs are necessary for visual circuit formation (Burgridge, 2014)
- Prenatal nicotine exposure alters the visual cortex system in baboons (Duncan, 2015).
- Even at a dose lower than that necessary to activate the receptor, nicotine causes desensitization of nAChRs (Wang, 2005), which results in a disturbance of normal synapse formations at the developmental stage (Slotkin, 2016).
In vitro study

Acetamiprid and Imidacloprid Alter the Gene Expression Profile of Neuron-Enriched Cultures from Neonatal Rat Cerebellum (Kimura-Kuroda 2016)

• long-term (14 days) exposure of neuron-enriched cultures
• low dose (1 μM) nicotine, acetamiprid or imidacloprid.
• A slight disturbance in Purkinje cell dendritic arborization was observed in the exposed cultures.

![Dendritic area comparison](image)
Moreover,

Significant differential expression (p<0.05, q<0.05, ≥1.5 fold) between control cultures versus nicotine-, acetamiprid-, or imidacloprid-exposed cultures in 34, 48, and 67 genes, respectively.

Common to all exposed groups were nine genes (four genes up, five genes down) essential for neurodevelopment.

Chronic neonicotinoid exposure alters the transcriptome of the developing mammalian brain in a similar way to nicotine exposure.

Overviews of gene expression changes in cerebellar cultures exposed to nicotine (NIC), acetamiprid (ACE), and imidacloprid (IMI) for 14 days.
Acetamiprid accumulates in special site of murine brain (Terayama 2016).

- Mospilan SP (18% acetamiprid + surfactant, dimethyl sulfoxide).
- Mice were fed by water for 3 to 7 days.
  - Normal: water
  - Vehicle: water with dimethyl sulfoxide
  - Acetamiprid: Mospilan (100-fold NOAEL acetamiprid)

Based on Terayama 2016.
**Acetamiprid Induces Abnormalities in Socio-Sexual and Anxiety-Related Behaviors of Male Mice (Sano 2016)**

- In utero and lactational Exposure, 0 mg/kg (control group), 1.0 mg/kg (low-dose group), or 10.0 mg/kg (high-dose group)

**Sexual Behavior**

- Anxiety-related behavior, as measured in the light-dark transition

No reductions in the testosterone level, the number of vasopressin-immunoreactive cells, or behavioral flexibility
Neo-nicotinic symptoms have been observed in Gunma, Japan, since 2004 (Taira 2006-2014)

Neo-nicotinic symptoms (NNS)

Subjective Symptoms
- Headache
- General fatigue
- Stomachache
- Chest pains/palpitation
- Muscle pain/weakness/spasm
- Cough

Objective Symptoms
- Postural tremor
- Recent memory loss
- Fever
First was Acetamiprid Spray in 2004 (Taira 2006)

- 0.02% acetamiprid aqueous solution was sprayed to a height of 40 m or higher above the ground, on mountainsides with air blast spraying equipment, for pine trees as a countermeasure against pine wilt disease.
Estimated exposure dose was max. 84.1μg/kg BW, 84% of ARfD (Ichikawa 2008)

### Demographic Data in 2004 and in 2005 (Taira 2014)

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sprayed Pesticide</td>
<td>Acetamiprid (+OP)</td>
<td>Acetamiprid</td>
</tr>
<tr>
<td>Sprayed period</td>
<td>5.26-6.28</td>
<td>5.17-6.24</td>
</tr>
<tr>
<td>Acetamiprid per area (μg/m²)</td>
<td>70</td>
<td>45</td>
</tr>
<tr>
<td>Number of patients</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Male/Female</td>
<td>20/58</td>
<td>18/45</td>
</tr>
<tr>
<td>Age</td>
<td>2-62</td>
<td>3-78</td>
</tr>
<tr>
<td>Under 15 years old</td>
<td>32 (50%)</td>
<td>15 (26%)</td>
</tr>
<tr>
<td>Electrocardiogram findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate abnormality(%)</td>
<td>32 (41%)</td>
<td>18 (29%)</td>
</tr>
</tbody>
</table>
After stop spraying in 2006, pandemic of NNS started. All of them became ill after continuous intake of tea beverages and conventional domestic fruits.

In 2004 acetamiprid spray: 78 patients

In 2005 acetamiprid spray: 63 patients

2006.8-2007.3: 1111 patients visited
We start to analyze patients’ urine. Several neonicotinoids and metabolites were identified (Taira et al. 2007-2011).

- Quantified by LC/MS
  - 6-Chloronicotinic acid, maximum 84.8 ng/mL
- Qualified by LC/TOFMS
  - Acetamiprid
  - 5-Hydroxy-imidaclorpid
  - 4,5-Dehydro-imidaclorpid
  - 4,5-Dihydroxy-imidaclorpid
  - N-Desmethyl-clothianidin
  - N-(2-Chlorothiazole-5-carboxyl)-glycine
- Quantified by LC/MS/MS
  - N-Desmethyl-acetetamiprid (DMAP), maximum 3.2 ng/mL
We conducted prospective case control study (Marfo 2015).

<table>
<thead>
<tr>
<th>Neo-nicotinic symptoms (NNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective NNS: headache • general fatigue • stomachache • chest pains/palpitation • muscle pain/weakness/spasm • cough</td>
</tr>
<tr>
<td>Objective NNS: Postural tremor • Recent memory loss • Fever</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TSG, n=19</th>
<th>ASG, n=16</th>
<th>NSG, n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 or 6 subjective NNS and Postural tremor (+) and Memory loss (+)</td>
<td>1-4 subjective NNS or Postural tremor (-) or Memory loss (-)</td>
<td>No NNS</td>
</tr>
</tbody>
</table>

TSG, n=19
ASG, n=16
NSG, n=50
# Demographic data of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>TSG</th>
<th>ASG</th>
<th>NSG</th>
<th>P value (TSG vs. NSG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>16</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/13</td>
<td>6/10</td>
<td>13/37</td>
<td>0.871</td>
</tr>
<tr>
<td>Age (y.o.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-10</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>15-49</td>
<td>8</td>
<td>6</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>65-</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>33.4 ± 21.0</td>
<td>30.9 ± 23.0</td>
<td>39.3 ± 20.1</td>
<td>0.287</td>
</tr>
<tr>
<td>min-max</td>
<td>5-69</td>
<td>5-78</td>
<td>4-87</td>
<td></td>
</tr>
</tbody>
</table>
DMAP and Thiamethoxam were more frequently detected in TSG. (prevalence odds ratio=14, 95% C.I. 3.5-57)
Recent memory loss diagnosed by food diary

Case A: 11 years old female could not recall what she ate for lunch two days ago or before; and DMAP was quantified at 3.6 nmol/mmol Cr in her urine.

<table>
<thead>
<tr>
<th>Meal</th>
<th>3 days before</th>
<th>2 days before</th>
<th>1 day before</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first</td>
<td></td>
<td></td>
<td>Rice, tea</td>
</tr>
<tr>
<td>The second</td>
<td></td>
<td></td>
<td>Rice, milk</td>
</tr>
<tr>
<td>The third</td>
<td>Isotonic water, meat dumpling</td>
<td></td>
<td>Rice, tea</td>
</tr>
</tbody>
</table>

Case B: 11 years old female without neo-nicotinic symptoms

<table>
<thead>
<tr>
<th>Meal</th>
<th>3 days before</th>
<th>2 days before</th>
<th>1 day before</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first</td>
<td>Rice, grilled egg, milk</td>
<td>Rice, sausage, milk, grilled egg</td>
<td>Rice, milk, grilled egg</td>
</tr>
<tr>
<td>The second</td>
<td>Buckwheat noodle, milk</td>
<td>Grilled beef rice, milk</td>
<td>Buckwheat noodle, yogurt drink</td>
</tr>
<tr>
<td>The third</td>
<td>Rice, grilled beef, milk</td>
<td>Rice, milk, vegetables, tuna &amp;Welsh onion</td>
<td>Curry and rice</td>
</tr>
</tbody>
</table>
Food intake reported by patients

【TSG】
- Tea beverage: DMAP/TMX detected (5), not detected (10)
- Fruits/vegetable juice: DMAP/TMX detected (2), not detected (8)
- Fruits: DMAP/TMX detected (1), not detected (9)
- Unknown: DMAP/TMX detected (1), not detected (8)

【ASG】
- Tea beverage: DMAP/TMX detected (5), not detected (10)
- Fruits/vegetable juice: DMAP/TMX detected (1), not detected (9)
- Fruits: DMAP/TMX detected (1), not detected (9)
- Unknown: DMAP/TMX detected (1), not detected (9)
Onset-First visit days (upper) & First visit-remission days (lower)

【TSG】

*reported by patients

【ASG】
Neonicotinoids are highly soluble to polar solvent.
- High value of acetone/water coefficient may predict accumulation in some part of body.
- Imidacloprid has moderate affinity with albumin and hemoglobin (Ding 2015)

<table>
<thead>
<tr>
<th>Solubility (g/L)</th>
<th>Water</th>
<th>Octanol</th>
<th>Acetone</th>
<th>$K_{aw}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamethoxam</td>
<td>4.1</td>
<td>0.62</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>Clothianidin</td>
<td>0.327</td>
<td>1.64</td>
<td>15.2</td>
<td>46</td>
</tr>
<tr>
<td>Acetamiprid</td>
<td>2.95</td>
<td>18.5</td>
<td>&gt;200</td>
<td>68</td>
</tr>
<tr>
<td>Imidaclorpid</td>
<td>0.48</td>
<td>0.78</td>
<td>47</td>
<td>98</td>
</tr>
<tr>
<td>Thiacloprid</td>
<td>0.185</td>
<td>3.36</td>
<td>64</td>
<td>346</td>
</tr>
<tr>
<td>Nitenpyram</td>
<td>840</td>
<td>192</td>
<td>290</td>
<td>0.35</td>
</tr>
<tr>
<td>Dinotefuran</td>
<td>40</td>
<td>58</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Sulfoxaflor</td>
<td>5.7</td>
<td>36.0</td>
<td>217</td>
<td>38</td>
</tr>
<tr>
<td>Flupyradifurone</td>
<td>3.2</td>
<td>250</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

Urinary excretion of imidacloprid and acetamiprid is slow (5μg oral, M/F=5/5, Harada 2016).

<table>
<thead>
<tr>
<th></th>
<th>Design</th>
<th>Bio-availability</th>
<th>r</th>
<th>$T_{1/2\alpha}$ (day)</th>
<th>$T_{1/2\beta}$ (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidacloprid</td>
<td>adult</td>
<td></td>
<td>0.13</td>
<td><strong>1.45</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rat blood(M/F)</td>
<td>100%</td>
<td>0.11/0.14 4.91/1.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clothianidin</td>
<td>adult</td>
<td></td>
<td>0.60</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rat (M/F)</td>
<td>89.2%</td>
<td>0.05/0.06 2.25/0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dinotefuran</td>
<td>adult</td>
<td></td>
<td>0.90</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rat (M/F)</td>
<td>98.5-98.9%</td>
<td>0.15/0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dm-Acetamiprid</td>
<td>adult</td>
<td></td>
<td>0.59</td>
<td>0.23</td>
<td><strong>1.65</strong></td>
</tr>
<tr>
<td></td>
<td>rat (M/F)</td>
<td>100%</td>
<td>no data</td>
<td>no data</td>
<td></td>
</tr>
</tbody>
</table>

$r$: Area under the curve (AUC), proportion excreted in urine.
Plausible Neonicotinoid Toxicokinetics

Neonicotinoids in Food, Beverage, and Air

High $K_{aw}$: 98

Moderate affinity: $10^4$ M$^{-1}$

2nd Peripheral Compartment (polar tissue, e.g. nAChRs)

Central Compartment

1st Peripheral Compartment (e.g. Alb, Hb)

Imidaclorprid: urine, feces, hair
$N$-Desmethyl-acetamiprid: urine, feces
Clothianidin: urine, feces
Dinotefuran: urine

Slow

Rapid
Detection rates of urinary neonicotinoids are increasing in Japan (Ueyama 2015). That of 3 y.o. is 58% (Osaka2016)
Autism and imidacloprid, a common flea and tick treatment for pets (Keil 2014)

- CHARGE (Childhood Autism Risks from Genetics and Environment) case-control study in CA, completed before 2011.
- The association between imidacloprid exposure and ASD warrants further investigation.
- This work highlights the need for validation studies regarding prenatal exposures in ASD.

### Epidemiological study 2

<table>
<thead>
<tr>
<th>Fetal/child age</th>
<th>Odds Ratio, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td></td>
</tr>
<tr>
<td>1–2yrs</td>
<td></td>
</tr>
<tr>
<td>2–3yrs</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted odds ratios and 95% confidence intervals comparing imidacloprid exposure of children with autism spectrum disorder with typically developing controls from the CHARGE data.
Other studies in CA, San Joaquin Valley

• Children who was born from 1997 to 2006
• Examined the mothers exposed to neonicotinoids within a 500 m radius of their address during a 3-month periconceptional window, and not exposed.

• Congenital heart defects (Carmichael et al. 2014)
  • 101 Tetralogy of Fallot and 785 non-malformed controls
  • Adjusted Odds Ratio (95% CI) was 2.4 (1.1–5.1)

• Anencephaly (Yang et al. 2014)
  • 73 anencephaly and 785 non-malformed controls
  • Adjusted Odds Ratio (95% CI) was 2.5 (0.9–7.1)
Process of Pesticide risk management

1. Collect evidence
   - case study, case report,
   - animal study, laboratory data, structure activity correlation

2. Find dose response relationship
   - Acute Reference Dose (ARfD, single dose)
   - Acceptable Dose of Intake (ADI, speed)

3. Evaluate the level of exposure

4. Assess the risk

WHO classified pesticide by acute toxicity in 2009. However, appropriate ADI setting may also protect children from the hazard of pesticides.
Lowest-observed-adverse-effect level (LOAEL) of neonicotinoids in human study

<table>
<thead>
<tr>
<th>Neonicotinoid</th>
<th>Exposure</th>
<th>Dose (μg/kg)</th>
<th>Matrix</th>
<th>Level (μg/L)</th>
<th>Current ADI (μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imidacloprid</td>
<td>Acute</td>
<td>8300</td>
<td>Blood</td>
<td>3</td>
<td>57</td>
</tr>
<tr>
<td>dm-Acetamiprid</td>
<td>Chronic</td>
<td></td>
<td>Urine</td>
<td>&lt; 0.6</td>
<td>71</td>
</tr>
<tr>
<td>Thiamethoxamam</td>
<td>Chronic</td>
<td></td>
<td>Urine</td>
<td>&lt; 0.3</td>
<td>18</td>
</tr>
</tbody>
</table>

- **Imidacloprid acute intoxication (Tamura 2002)**
  - 95 y.o. male, entubated, gastric lavage in ER
  - 2% formula 25 mL, oral (8300 μg/kg)
  - LOAEL = 8300 μg/kg
  - ARfD = 8300/10/10 = 83 μg/kg
  - ADI = ARfD/10 = 8.3 μg/kg = <15% of current ADI
Why urinary excretion is low in chronic exposure?

Acute exposure

2\textsuperscript{nd} Peripheral
\textgreater 3 \sim 300

Central
3

1\textsuperscript{st} Peripheral
300

Urine

Chronic exposure

2\textsuperscript{nd} Peripheral
30

Central
0.3

1\textsuperscript{st} Peripheral
30

Urine
What we can do to reduce environmental neonicotinoids exposure?

- Reduce ADI?
- Share ADI with all neonicotinoids?
- Ban all?
- Restrict the application?
- Stop seed treatment by neonicotinoids?
- Use alternatives?
- Go organic for sustainable agriculture?

- It is the time we stop the challenge test on child brain.
Conclusion

- Recent animal studies and in vitro studies suggest neonicotinoids may cause neurodevelopmental disorders.
- We have several human evidence about the health effect of neonicotinoid by environmental exposure.
- Acceptable Dose of Intake of neonicotinoids needs to be revised to protect children from neurodevelopment disorders.
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http://www.mext.go.jp/a_menu/shotou/tokubetu/material/__icsFiles/afieldfile/2015/03/27/1356210.pdf

https://www.epa.gov/ace


Background 1 (continued)


Background 2


Background 3


http://www.cdpr.ca.gov/docs/mill/nopdsold.htm

Background 4


In vitro study


Animal study


Clinical study


Toxicological study


[www.acis.fanic.go.jp/shoroku/acetamiprid/adeamiprid_05.pdf](http://www.acis.fanic.go.jp/shoroku/acetamiprid/adeamiprid_05.pdf)
[www.acis.fanic.go.jp/shoroku/thiamethoxam/thiamethoxam_05.pdf](http://www.acis.fanic.go.jp/shoroku/thiamethoxam/thiamethoxam_05.pdf)


Epidemiological study


Regulation

