Recall of Valsartan-containing products

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Outline

- Press release related to recall for valsartan-containing products
  - Europe
  - US
  - Indonesia
- N-nitrosodimethylamine (NDMA) overview

Europe

- July 5th 2018,
  - EMA reviewing medicines containing valsartan from Zhejiang Huahai following detection of an impurity (NDMA).
  - MHRA UK :recalling all batches of valsartan containing medicines made by Actavis Group PTC (now Accord) and Dexcel Pharma Ltd due to contamination.
- July 17th 2018,
  - EMA gathering details of the company's manufacturing processes, following changes introduced in 2012 that are believed to have produced NDMA as a side product.

- 2 Agt 18,
  - EMA is doing preliminary assessment of possible risks to patients.
    - Estimation: one extra case of cancer for every 5,000 patients taking the affected medicines at the highest valsartan dose (320 mg) every day for 7 years [(based on average levels of this impurity detected in the active substance from Zhejiang Huahai Pharmaceuticals (60 parts per million)].
      - Extrapolated from animal studies and should be considered in the context of the lifetime risk of cancer in the EU and NDMA exposure from other sources.
      - Assumption: NDMA present in the active substance is carried over in the final product in the same amount.

- 10 Agt 2018
  - low levels of N-nitrosodimethylamine (NDMA) have been detected in the valsartan active substance manufactured by a second company, Zhejiang Tianyu.
  - The NDMA levels detected in batches of valsartan from Zhejiang Tianyu is much lower than levels seen in the active substance from Zhejiang Huahai
- 20 Agt 2018
  - The suspension of the certificate by the European Directorate for the Quality of Medicines and Healthcare.
  - Zhejiang Huahai and Zhejiang Tianyu are no longer authorize to supply valsartan active substance in EU.

US (FDA)

- July 13th 2018
  - FDA announced a recall of certain batches of valsartan tablets because of an impurity, a chemical known as N-nitrosodimethylamine (NDMA).
- July 18 2018
  - Updating list of valsartan-containing products that are being recalled
  - The presence of NDMA is related to changes in the way the active substance was manufactured. Some levels of the impurity may have been in the valsartan-containing products for as long as four years.
- July 24, 2018
  - FDA publish list of valsartan -containing products not included in the recall

- July 27, 2018
  - FDA updating list of valsartan –containing products that are being recalled (adding lists from repackaging companies)
  - FDA analysis of NDMA levels in recalled valsartan in the US.
    - US EPA: consuming up to 96ng NDMA/day is considered safe – with this amount during a person's life time would result in less than one additional case of cancer for every 100,000 people (<1:100.000).
    - Some levels of the impurity may have been in the valsartan-containing products for as long as four years.
    - The estimation that if 8,000 people took the highest valsartan dose (320 mg) from the recalled batches daily for the full four years, there may be one additional case of cancer over the lifetimes of these 8,000 people (1:8000)

- August 2, 2018
  - Updating list of products included in the recall and not included in the recall
  - Reminding API manufacturers to evaluate process of API manufacturing for unsafe impurities.
- August 9, 2018
  - Updating list of products included in the recall and not included in the recall
  - Recall of valsartan-containing products manufactured by Hetero Labs limited in India (using similar process similar to Zhejiang Huahai Pharmaceuticals, although the level is lower)

- August 20, 2018
  - Updating list of products included in the recall and not included in the recall.
  - Providing information on NDMA levels in some foods
- August 22, 2018
  - Updating list of products included in the recall and not included in the recall.
  - Release analytical method to detect NDMA (GC/MS headspace method) in valsartan API and finished products,

Indonesia (BPOM)

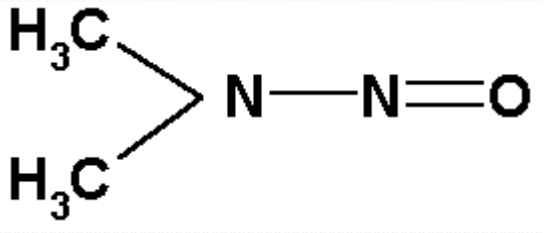
- July 12, 2018
  - Announce valsartan recall following EMA announcement
  - List of valsartan-containing product-API from Zhejiang Huahai:
    - Varten tablet 80mg, 160 mg (PT Actavis Indonesia)
    - Valesco kaplet salut selaput 40mg, 80mg, 160mg (PT Dipa Pharmalab Intersains)

Indonesia (BPOM)

- List of valsartan-containing products -API not from Zhejiang Huahai:
  - Valsartan, Valdix (Dexa Medica)
  - Valsartan (Etercon)
  - Valsif (Ferron), Diovan
  - Co-Diovan, Exforge, Uperio (Novartis)
  - Tyoval (Novell)

N-nitrosodimethylamine (NDMA)

N-nitrosodimethylamine (NDMA) who



- *N-Nitrosodimethylamine (NDMA) is the simplest* dialkylnitrosamine.
- Volatile, combustible, yellow, oily liquid.
- Susceptible to photolytic breakdown due to its absorption of ultraviolet light

- Sources:
  - major releases of NDMA have been from the manufacture of pesticides, rubber tires, and dyes.
  - may also form under natural conditions in air, water, and soil as a result of chemical, photochemical, biological processes .
  - Also detected in drinking-water and in automobile exhaust.

- Human exposure
  - Occupational: rubber, tannery, fish processing, dye, and surfactant industries.
  - Food ingestion (e.g., cured meat products,smoked fish, cheeses, pickled and salt-preserved foods, low-fat dried milk products).
  - drinking contaminated water
  - breathing cigarette smoke and contaminated ambient air
  - etc

- Acute Effects:
  - Liver damage in humans, with symptoms that include nausea, vomiting, headaches, and malaise.
  - Hematological and severe liver effects (hemorrhagic necrosis) were reported in animals acutely exposed via inhalation and ingestion.

- Chronic Effects (Non-cancer):
  - Chronic exposure of humans to N-nitrosodimethylamine may cause liver damage (jaundice and swelling)and low platelet counts.
  - Chronic oral exposure has resulted in severe liver damage in animals.

- Reproductive/Developmental Effects:
  - No information is available on the reproductive or developmental effects of NDMA in humans.
  - Increased fetal mortality was observed but no birth defects were noted in rats.
  - Has been shown to cause cancer in the offspring of rats, mice, and hamsters.

- Cancer Risk:
  - Limited data from human studies because human exposure to nitrosamines generally results from contact with mixtures of these compounds.
  - Carcinogenic in a number of animal species, inducing tumors in various organs and by various routes of exposure.
  - Increased incidences of liver, kidney, and lung tumors in rats and mice.

Song P, Wu L and Guan W. Dietary Nitrates, Nitrites, and Nitrosamines Intake and the Risk of Gastric Cancer: A Meta-Analysis. Nutrients . 2015;7:9872–9895

- **Description of studies**
  - 11 studies on NDMA (7 cohort, 4 case-control)
  - Mostly conducted in Europe (Italy, France, Netherlands, Sweden, Finnish, European), and Uruguay.

- **Dietary NDMA intake and risk of cancer**
  - RR for high vs low intake was 1.34 (95%CI 1.02-1.76) with obvious evidence of heterogeneity (I^2=75.8%, p<0.001)

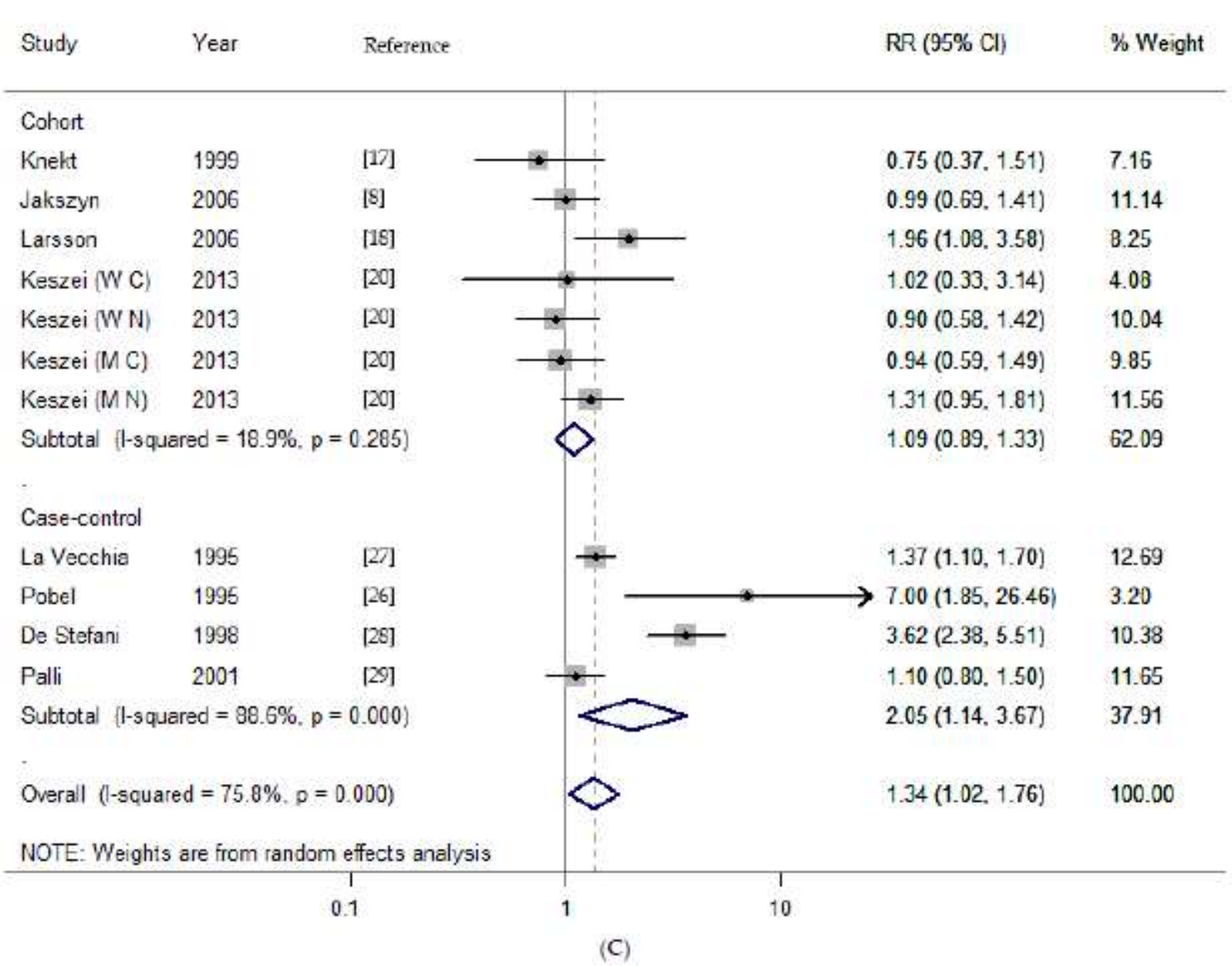
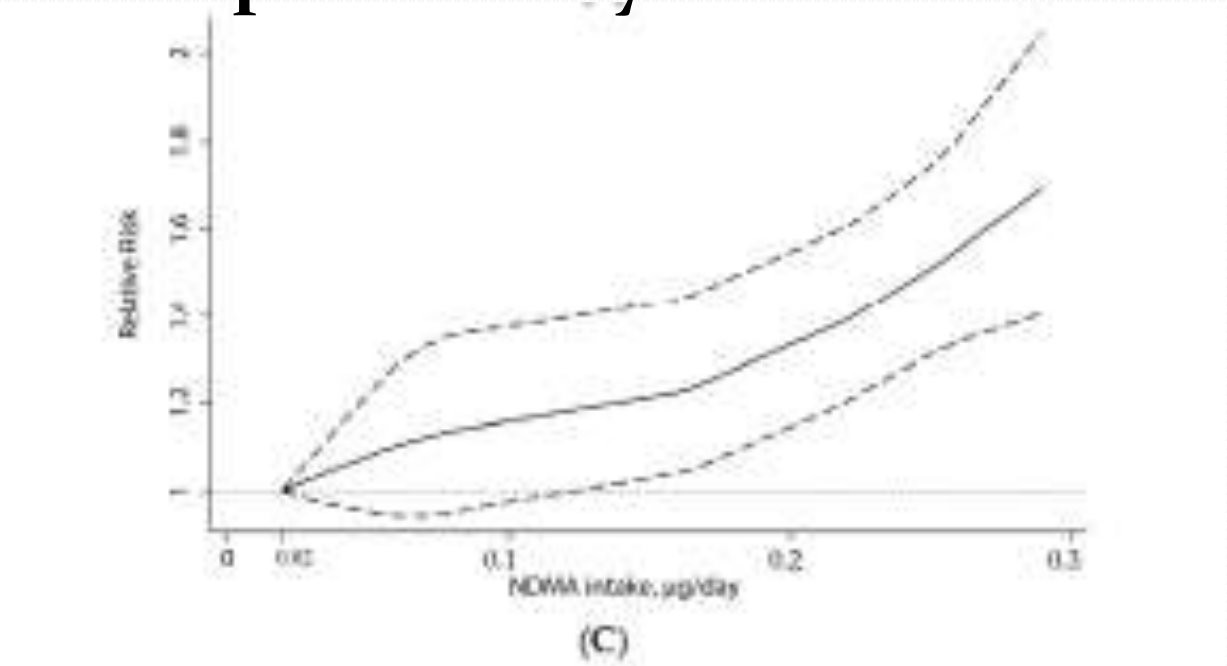


Figure 2. Dietary nitrates, nitrites and NDMA intake and the risk of gastric cancer for the highest *versus* lowest categories. (**A**) nitrates; (**B**) nitrites; (**C**) NDMA. (C, cardia; N, non-cardia; M, male; W, women).

- **Dose response analysis**



(C)

- 7 studies were included
- Non linear trend toward gastric cancer risk with increasing NDMA intake following an increase in the risk of NDMA intake up to 0.12 mcg/day.

- **Conclusion of the article:**
  - Increase consumption of NDMA, increase risk of gastric cancer

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